# Bale/Doneen Live Chat Session

5/14/2014

5:30-6:30 pm PST

Bradley Bale, MD

# Dr. Amy Lynn Doneen

## Congratulations!!!

# Intention of the live chats

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

# New Studies??!!!: OMG!


Never ending! ☺

# What about the latest stats?

# Sudden Cardiac Death Most Costly Health Condition

- ~ 213,000 SCDs in US annually
- Total years of productive life lost (YPLL) from SCD for men ~ 2.04 million (95% uncertainty interval, 1.86–2.23 million)
- Total YPLL from SCD for women ~1.29 million (95% uncertainty interval, 1.13–1.45 million)

Stecker, E. C., et. al. (2014). Public Health Burden of Sudden Cardiac Death in the United States. *Circulation: Arrhythmia and Electrophysiology, 7*(2), 212-217.

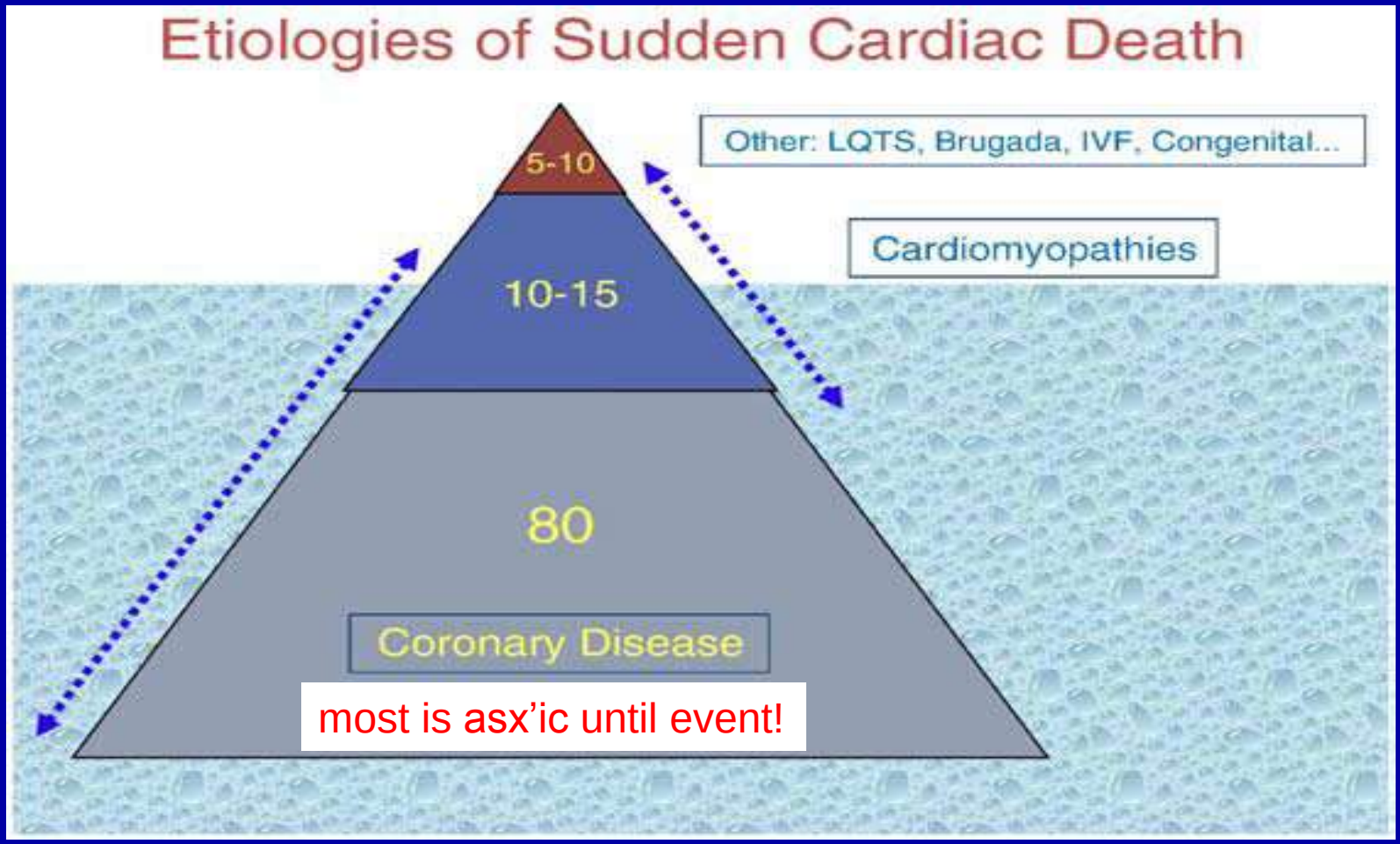
# Sudden Cardiac Death Most Costly Health Condition

- SCD was responsible for a greater burden of premature death than all individual cancers for each sex.

- Men aged <65 years, YPLL from SCD was more than double that from any individual cancer.

Stecker, E. C., et. al. (2014). Public Health Burden of Sudden Cardiac Death in the United States. *Circulation: Arrhythmia and Electrophysiology, 7*(2), 212-217.

# CAD Causes the Vast Majority of Sudden Cardiac Death



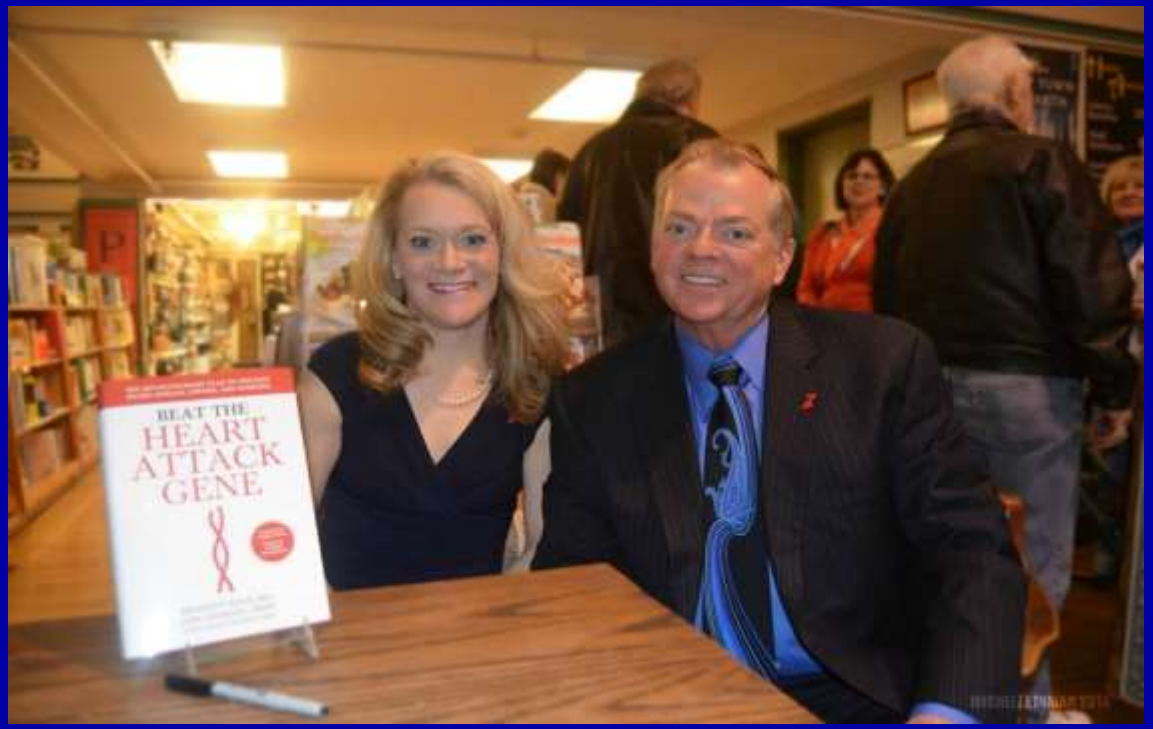

Chugh, S. S., et. al. (2008). Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis, 51*(3), 213-228.

# SCD: What do they propose as a solution??

Designing and evaluating emergency medical response systems and automatic external defibrillator deployments

Optimizing implantable cardioverter-defibrillators and developing new methods targeting arrhythmic death prevention.

Stecker, E. C., et. al. (2014). Public Health Burden of Sudden Cardiac Death in the United States. *Circulation: Arrhythmia and Electrophysiology, 7*(2), 212-217.




# What??!!!! – how about preventing CAD or treating it before it is evident!!*

Bale BF, Doneen AL (2014) A Guarantee of Arterial Wellness: New Era of Cardiovascular Medicine. J Clin Exp Cardiolog 5:298. doi: 10.4172/2155-9880.1000298

# Red Flags

# Geomagnetic Storms May Elevate BP

- 447 unrx'ed pts; 24-h BP monitoring; 5 yrs. ; evaluated for association with geomagnetic K-sum (measurement -geomagnetic field caused by solar particle radiation).

- Significant correlation seen with systolic and diastolic BP; higer BP with greater disturbance.

Ghione, S., Mezzasalma, L., Del Seppia, C., & Papi, F. (1998). Do geomagnetic disturbances of solar origin affect arterial blood pressure? *J Hum Hypertens, 12*(11), 749-754.

# Geomagnetic Storms May Elevate BP

- Difference between the quietest and the most disturbed days was 6 to 8 mm Hg for 24-h systolic and diastolic BP.

- Why???- increase in the ‘vulnerability’ of subjects to everyday life stress through endorphinergic pathways.????

Ghione, S., Mezzasalma, L., Del Seppia, C., & Papi, F. (1998). Do geomagnetic disturbances of solar origin affect arterial blood pressure? *J Hum Hypertens, 12*(11), 749-754.

# Geomagnetic Activity (GMA) and CV Risk: Mechanisms?

Instant hemodynamic effects of GMA: RBS are extremely sensitive; increased platelet aggregation, blood coagulation and spasm in the afferent vessels of the microcirculatory.

Shaposhnikov, D., et. al. (2013). The influence of meteorological and geomagnetic factors on acute myocardial infarction and brain stroke in Moscow, Russia. *Int J Biometeorol*. doi: 10.1007/s00484-013-0660-0

Gurfinkel YI, Voeikov VL (2006) Solar activity effects on blood of patients with coronary heart disease. In: Atkov OY, Gurfinkel YI (eds) Proceedings of International Scientific Workshop «Space weather effects on biological systems and human health». Reprocenter, Moscow, pp 101–103

# Geomagnetic Storms Increase Stroke Risk

- Pts from International Stroke Incidence Studies Data Pooling Project; subjects ≥16 yo; only first in life time strokes included; geomagnetic activity was obtained from the World Data Center and National Oceanic and Atmospheric Administration Space Environment Center.

- Geomagnetic storms categorized into 3 groups: moderate (60–99 Ap Index), strong (100–149 Ap Index), and severe/extreme (150+ Ap index).

Feigin, V. L., et. al. (2014). Geomagnetic Storms Can Trigger Stroke: Evidence From 6 Large Population-Based Studies in Europe and Australasia. *Stroke*. doi: 10.1161/STROKEAHA.113.004577

# Geomagnetic Storms Increase Stroke Risk

- 11,453 strokes during 23 yrs (1981–2004); ~ 50% of strokes in females; mean age 70; ~ 25% undetermined type of stroke.

- Significant direct association with intensity of geomagnetic activity and stroke incidence.

- Ap Index 60+ associated with 19% increase in the risk of stroke (95% CI-11%–27%); effect was more pronounced in people <65 yo

Feigin, V. L., et. al. (2014). Geomagnetic Storms Can Trigger Stroke: Evidence From 6 Large Population-Based Studies in Europe and Australasia. *Stroke*. doi: 10.1161/STROKEAHA.113.004577

# Geomagnetic Storms Increase Stroke Risk

- Geomagnetic storms can account for 2.64% of all strokes.
- The association is independent of other known and unknown cardiovascular risk factors.
- 16.9 million new annual strokes globally; ~ 500,000 could be attributed to geomagnetic storms.

Feigin, V. L., et. al. (2014). Geomagnetic Storms Can Trigger Stroke: Evidence From 6 Large Population-Based Studies in Europe and Australasia. *Stroke*. doi: 10.1161/STROKEAHA.113.004577

# Geomagnetic Storms Increase Stroke Risk

- There was a 7 day delay triggering stroke occurrence of any pathological type.
- May be due to geomagnetic activity increasing BP.
- Ischemic stroke risk may be due the effect of geomagnetic activity on heart rate and blood viscosity/coagulability.

Feigin, V. L., et. al. (2014). Geomagnetic Storms Can Trigger Stroke: Evidence From 6 Large Population-Based Studies in Europe and Australasia. *Stroke*. doi: 10.1161/STROKEAHA.113.004577

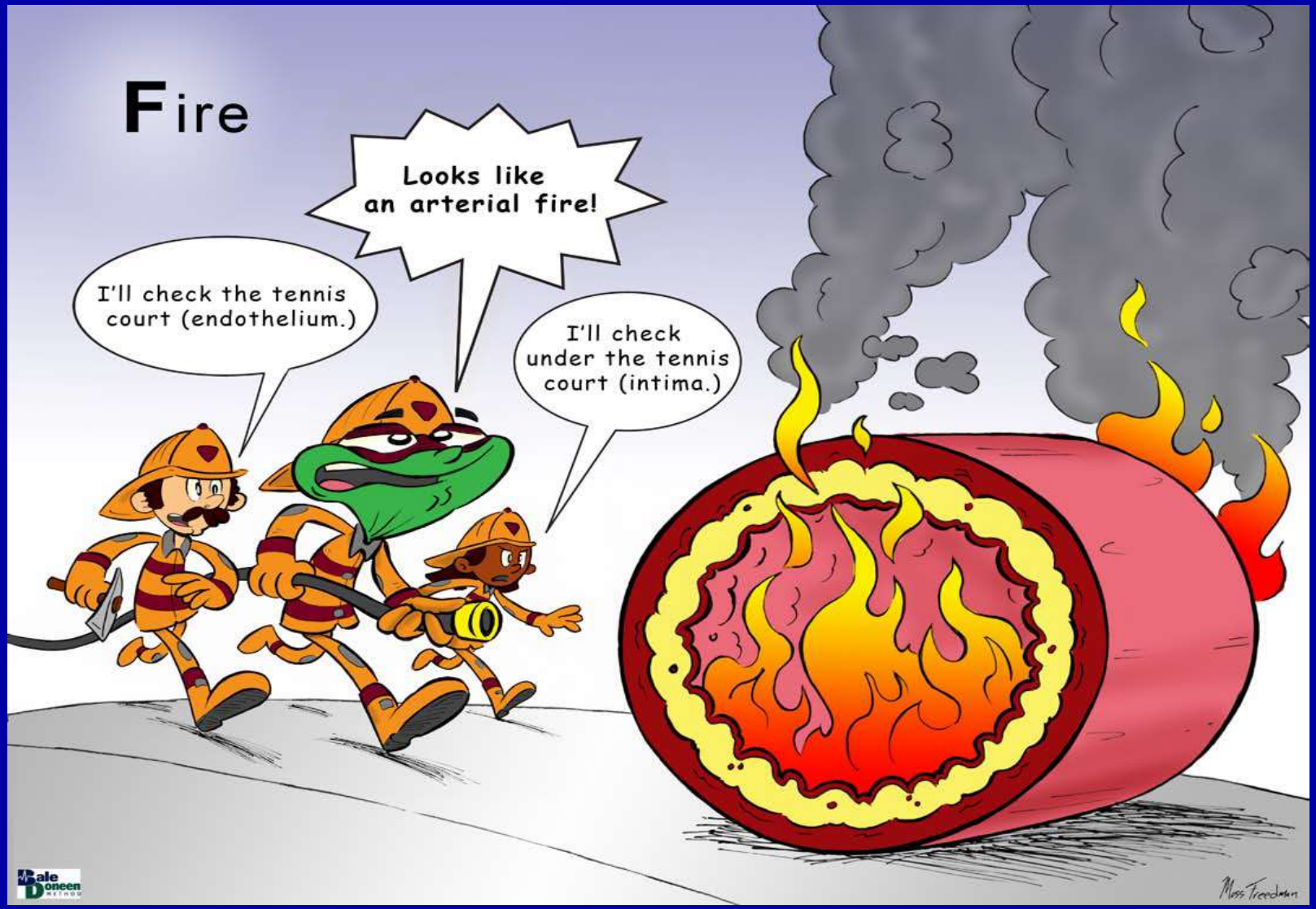
# Geomagnetic Storms Increase Stroke Risk

Study implies that tighter control of conventional stroke risk factors during the days preceding geomagnetic storms may reduce stroke incidence.

BDM thought: always maintain cold arteries and an excellent BP.

Feigin, V. L., et. al. (2014). Geomagnetic Storms Can Trigger Stroke: Evidence From 6 Large Population-Based Studies in Europe and Australasia. *Stroke*. doi: 10.1161/STROKEAHA.113.004577

# Inflammation



# What?? STABILITY Trial Surprising

# STABILITY Trial Study Design

**Patients with chronic CHD**
(prior MI >1 mth, prior coronary revascularization, multivessel CAD)

Enrichment criteria: ≥60 years of age, diabetes mellitus, low HDL, current smoking, significant renal dysfunction, polyvascular disease

15,828 patients randomized

Darapladib 160mg daily

Placebo

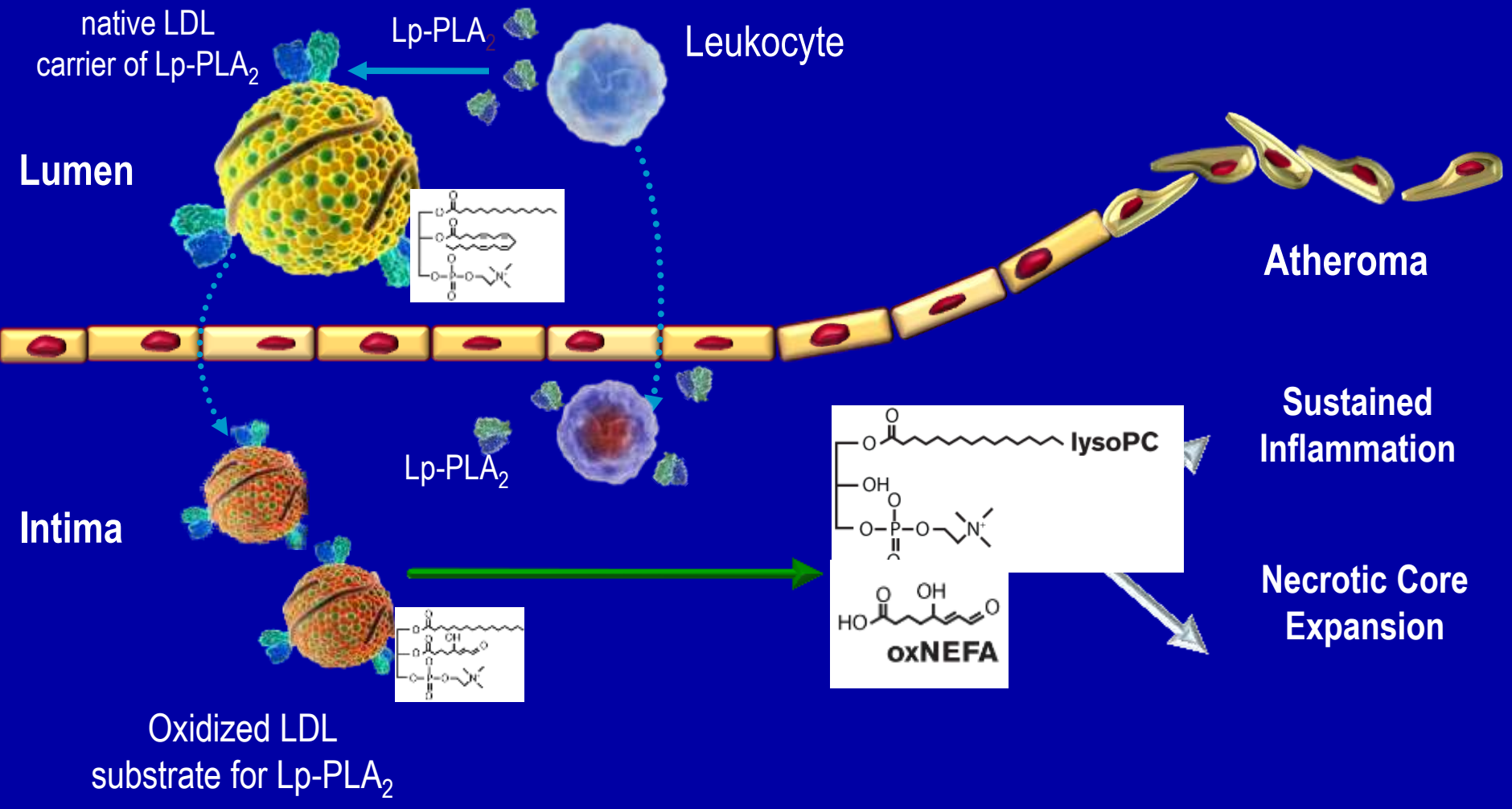
Optimized guideline-recommended treatment

Median follow-up 3.7 years, 1588 events

Primary endpoint: composite of CV death, MI, stroke
Secondary endpoints: major coronary events, total coronary events

Design paper reference: White H, et al. Am Heart J 2010;160:655-61.

# Lipoprotein- associated Phospholipase $A_2$ (Lp-$PLA_2$) activity: Background for study!




Macphee, *Biochem J* 1999; Zalewski and Macphee, *ATVB* 2005; Shi *Atherosclerosis* 2007; Kolodgie, *ATVB* 2006

# 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
- 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

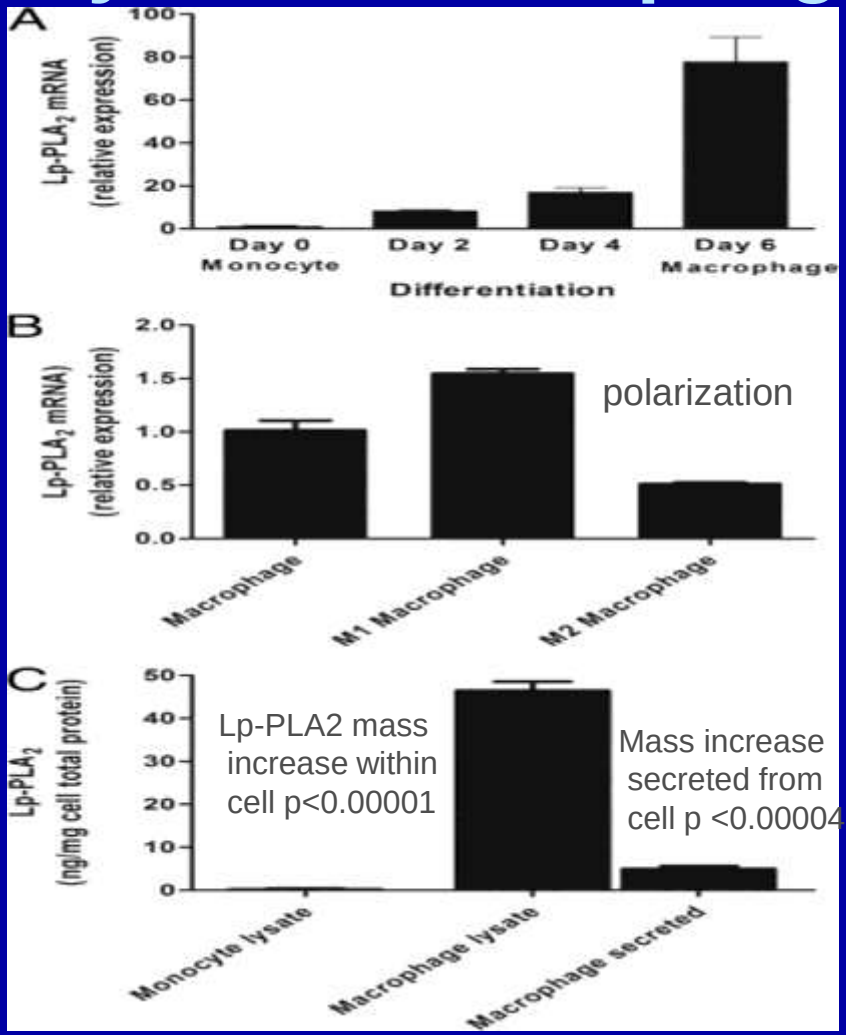
**Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772**

# Lp-PLA2 Increases in Inflammatory Macrophages in Vitro

- Same subjects
- Monocytes were isolated and transitioned into macrophages over six days (using LPS)
- Macrophages were polarized into M1 or M2

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

# Lp-PLA2 Increases During Differentiation of Human Monocytes to Macrophages In Vitro




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

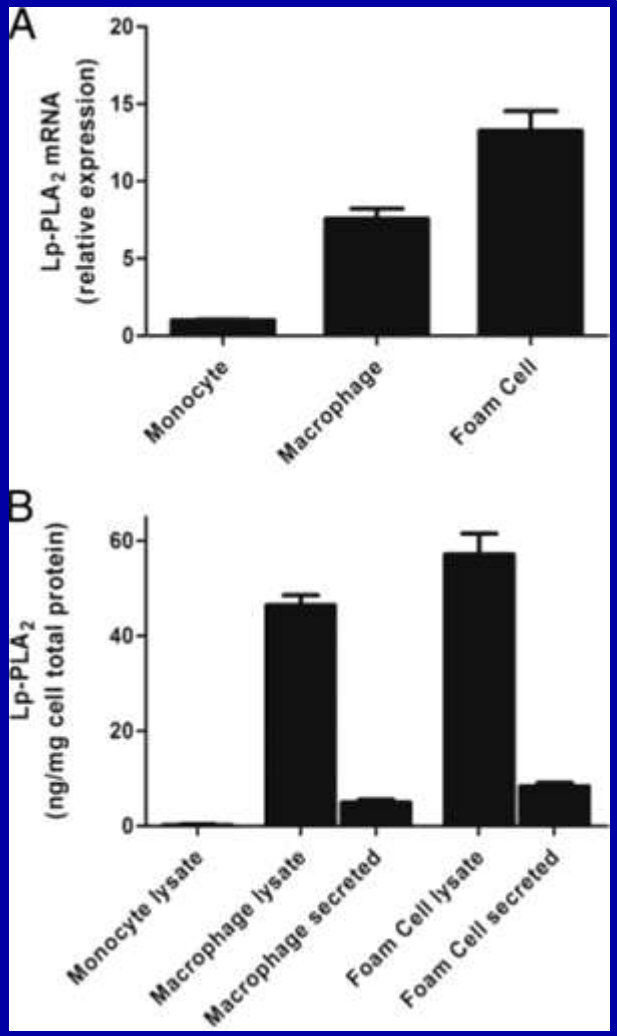
JACC Journal of the American College of Cardiology

# Lp-PLA2 Increases in ‘Foam Cells’ in Vitro

- Macrophages exposed to oxidized LDL-C for 48 hrs
- Induced ‘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 generated by macrophages and foam cells in the wall of artery 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

Dale Doneen Method

# BDM Thoughts

With this knowledge any trial trying to show benefit of a medication that blocks Lp-PLA2 activity should use a population with high Lp-PLA2 levels in the wall = active dangerous disease; certainly NOT stable disease

# BDM Thoughts

Optimal medical therapy should result in relatively ‘stable’ arterial disease = low levels of Lp-PLA2

If Lp-PLA2 is not elevated, blocking its activity should not provide any significant benefit!

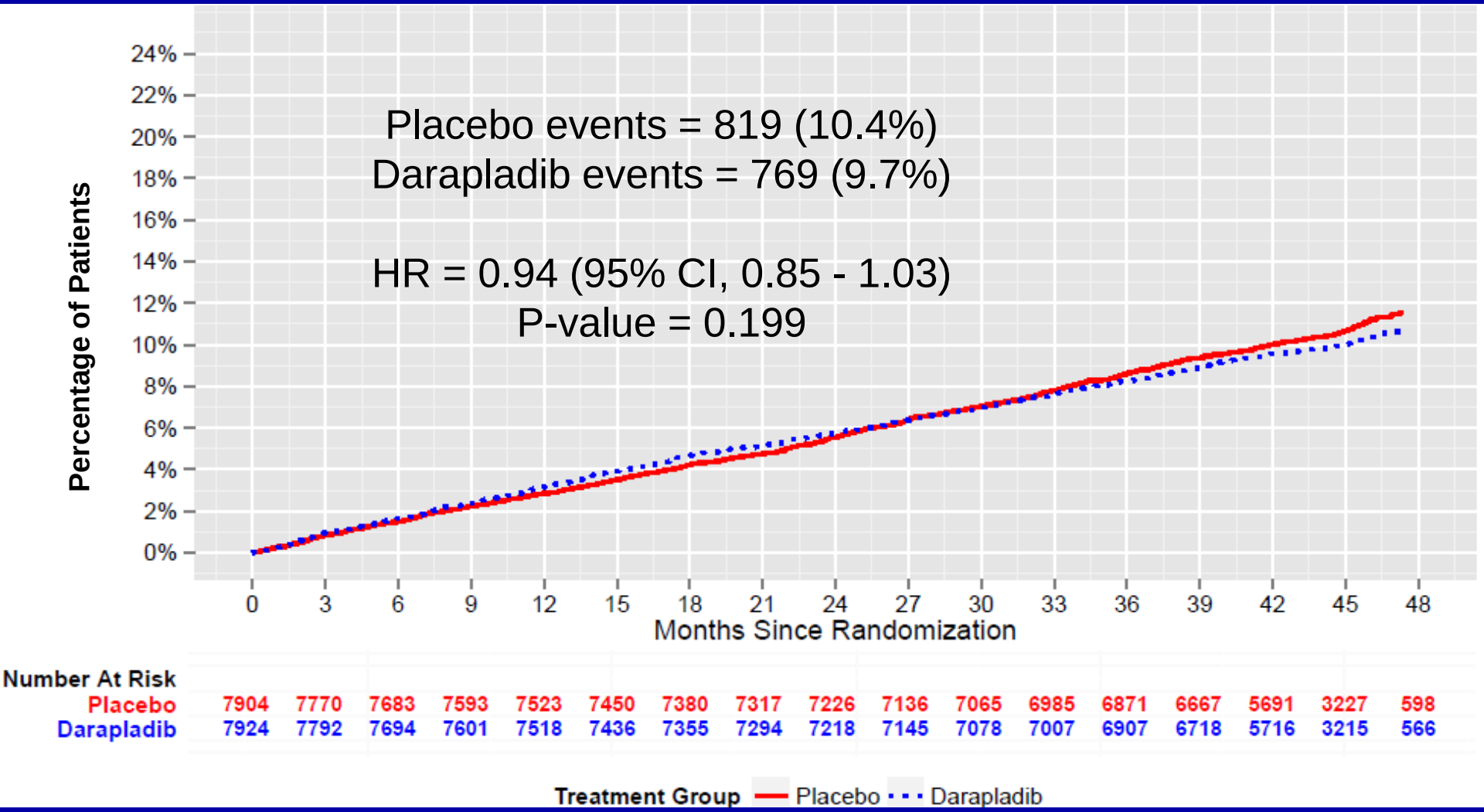
Since there is a significant correlation between the serum levels and arterial wall levels of Lp-PLA2, correlation of trial results with those levels is critical.

# High Standard of Care

| | Time Point | Placebo | Darapladib |
|---|---|---|---|
| Aspirin | Baseline<br>Study end | 93%<br>91% | 92%<br>90% |
| Statins | Baseline<br>Study end | 97%<br>96% | 97%<br>96% |
| Beta-Blockers | Baseline<br>Study end | 79%<br>79% | 79%<br>78% |
| ACE inhibitor | Baseline<br>Study end | 56%<br>54% | 57%<br>54% |
| Angiotensin II receptor blocker | Baseline<br>Study end | 23%<br>27% | 22%<br>26% |

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# Primary Endpoint: Time to First Occurrence of CV Death, MI, Stroke



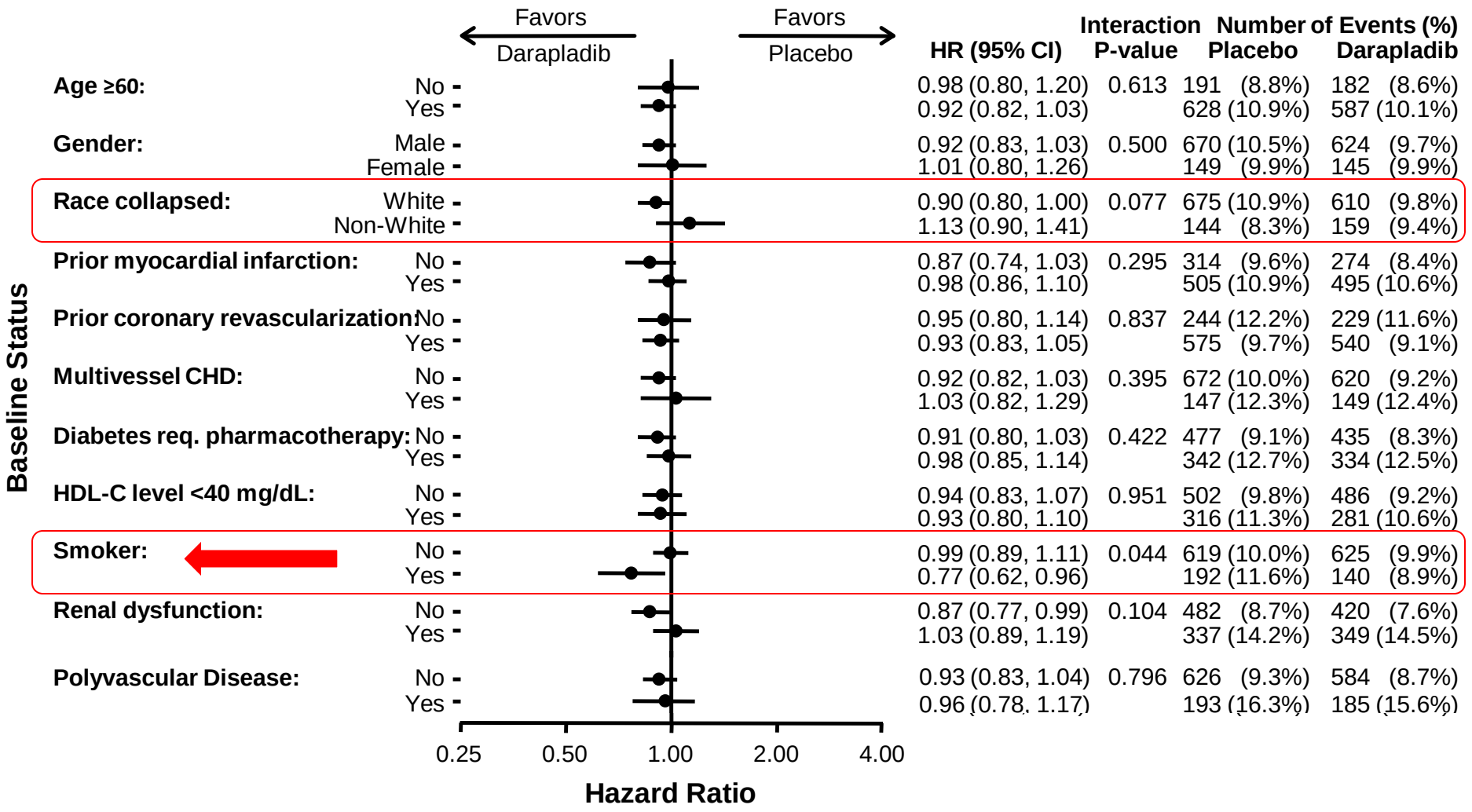

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# BDM Thoughts

Optimal medical management will not suppress the inflammation and active ASVD resulting from smoking.

Smokers would be a population in which you would expect to see benefit from darapladib.

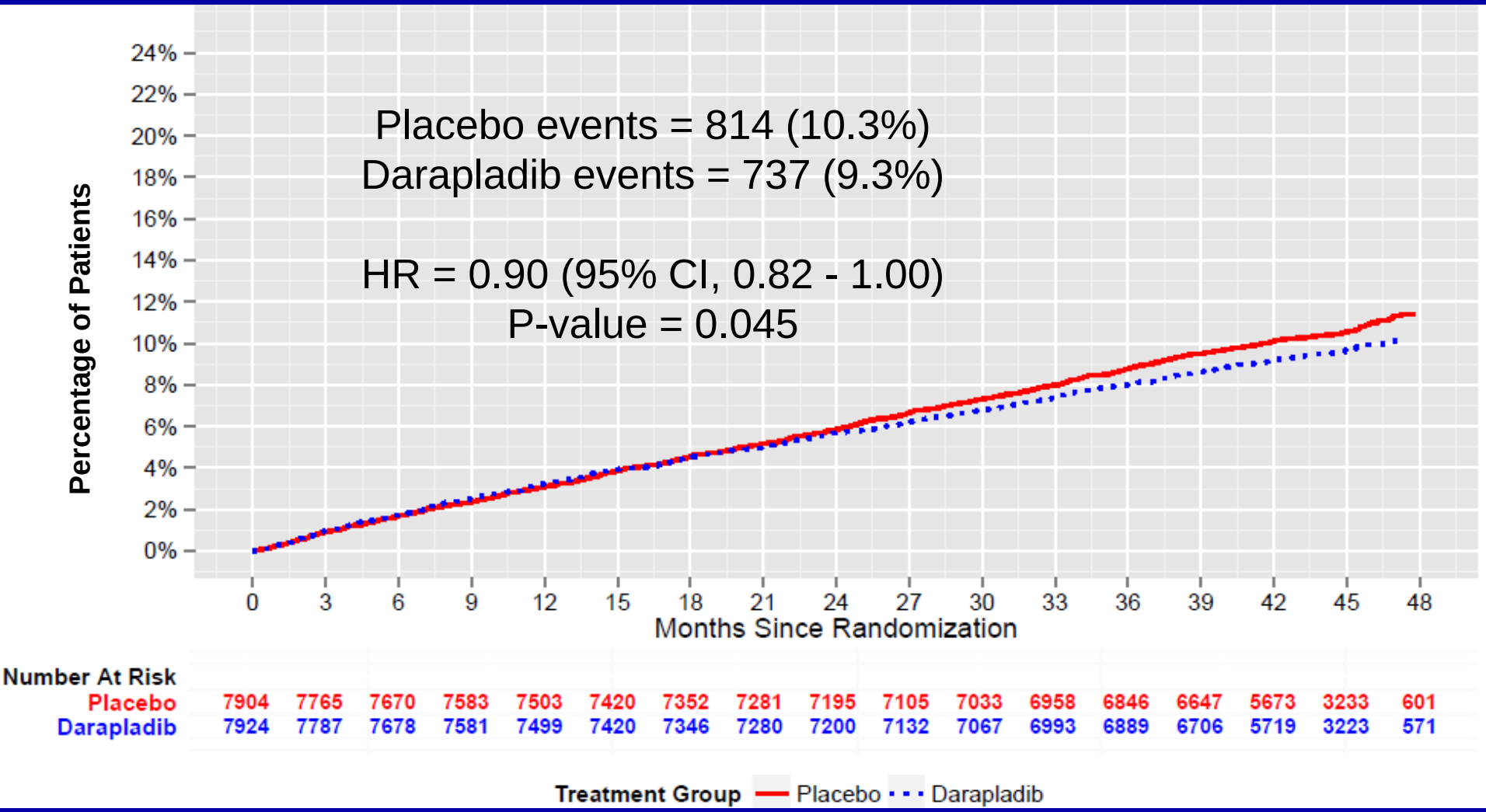
# Subgroup Analyses for CV Death, MI, Stroke




| Baseline Status | | HR (95% CI) | Interaction P-value | Number of Events (%) Placebo | Darapladib |
|---|---|---|---|---|---|
| **Age ≥60:** | No | 0.98 (0.80, 1.20) | 0.613 | 191 (8.8%) | 182 (8.6%) |
| | Yes | 0.92 (0.82, 1.03) | | 628 (10.9%) | 587 (10.1%) |
| **Gender:** | Male | 0.92 (0.83, 1.03) | 0.500 | 670 (10.5%) | 624 (9.7%) |
| | Female | 1.01 (0.80, 1.26) | | 149 (9.9%) | 145 (9.9%) |
| **Race collapsed:** | White | 0.90 (0.80, 1.00) | 0.077 | 675 (10.9%) | 610 (9.8%) |
| | Non-White | 1.13 (0.90, 1.41) | | 144 (8.3%) | 159 (9.4%) |
| **Prior myocardial infarction:** | No | 0.87 (0.74, 1.03) | 0.295 | 314 (9.6%) | 274 (8.4%) |
| | Yes | 0.98 (0.86, 1.10) | | 505 (10.9%) | 495 (10.6%) |
| **Prior coronary revascularization:** | No | 0.95 (0.80, 1.14) | 0.837 | 244 (12.2%) | 229 (11.6%) |
| | Yes | 0.93 (0.83, 1.05) | | 575 (9.7%) | 540 (9.1%) |
| **Multivessel CHD:** | No | 0.92 (0.82, 1.03) | 0.395 | 672 (10.0%) | 620 (9.2%) |
| | Yes | 1.03 (0.82, 1.29) | | 147 (12.3%) | 149 (12.4%) |
| **Diabetes req. pharmacotherapy:** | No | 0.91 (0.80, 1.03) | 0.422 | 477 (9.1%) | 435 (8.3%) |
| | Yes | 0.98 (0.85, 1.14) | | 342 (12.7%) | 334 (12.5%) |
| **HDL-C level <40 mg/dL:** | No | 0.94 (0.83, 1.07) | 0.951 | 502 (9.8%) | 486 (9.2%) |
| | Yes | 0.93 (0.80, 1.10) | | 316 (11.3%) | 281 (10.6%) |
| **Smoker:** | No | 0.99 (0.89, 1.11) | 0.044 | 619 (10.0%) | 625 (9.9%) |
| | Yes | 0.77 (0.62, 0.96) | | 192 (11.6%) | 140 (8.9%) |
| **Renal dysfunction:** | No | 0.87 (0.77, 0.99) | 0.104 | 482 (8.7%) | 420 (7.6%) |
| | Yes | 1.03 (0.89, 1.19) | | 337 (14.2%) | 349 (14.5%) |
| **Polyvascular Disease:** | No | 0.93 (0.83, 1.04) | 0.796 | 626 (9.3%) | 584 (8.7%) |
| | Yes | 0.96 (0.78, 1.17) | | 193 (16.3%) | 185 (15.6%) |

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

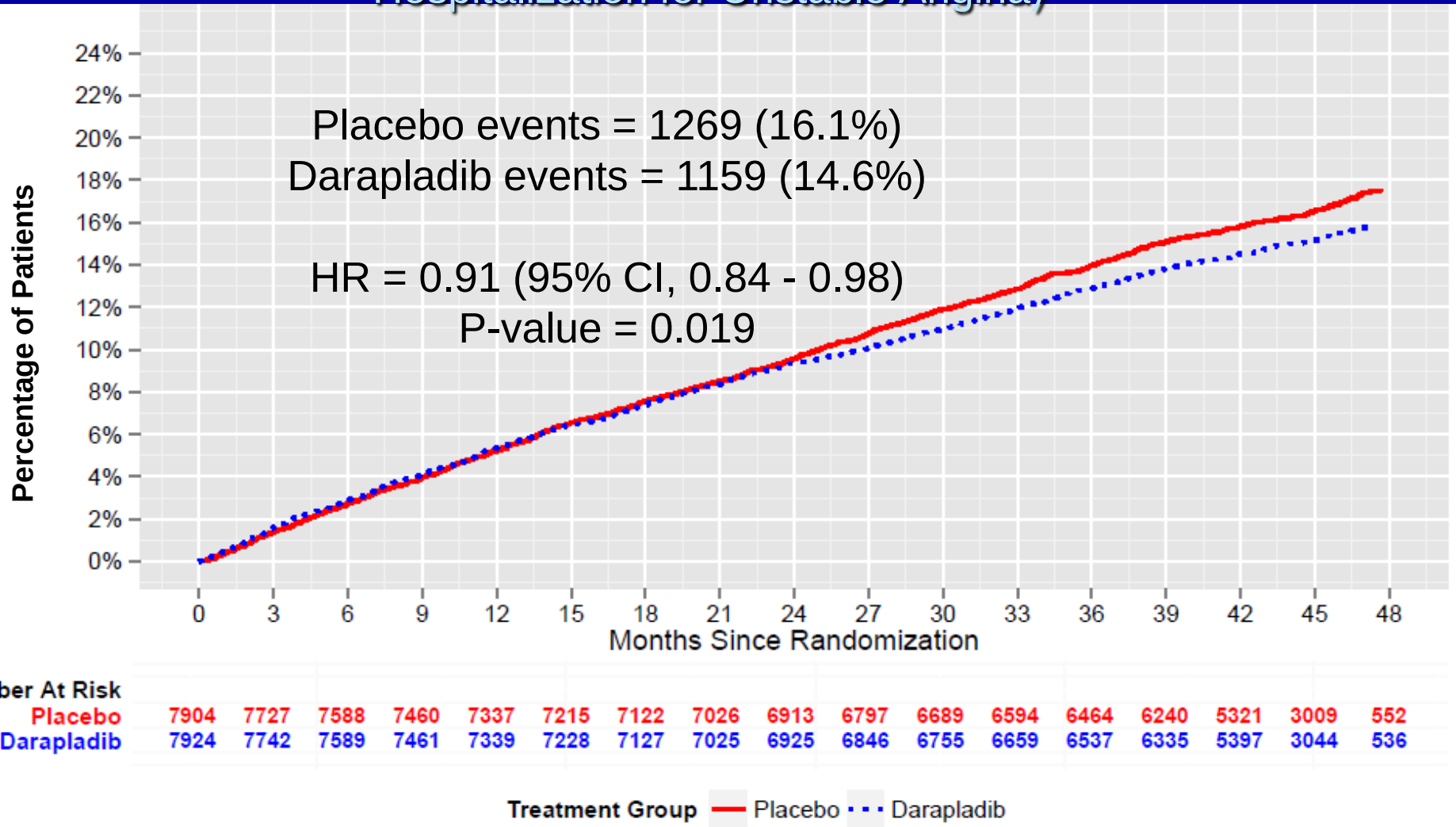
# Time to First Occurrence Major Coronary Events
## (CHD Death, MI, Urgent Coronary Revascularization)




Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# Time to First Occurrence Total Coronary Events

## (CHD Death, MI, Any Coronary Revascularization, Hospitalization for Unstable Angina)




Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# Adverse Events

| | Placebo (N=7890) | Darapladib (N=7912) |
|---|---|---|
| Any serious adverse event | 44% | 43% |
| Any adverse event leading to study drug discontinuation | 14% | 20% |
| Cancer | | |
| New cancer | 6.7% | 6.4% |
| Adjudicated new GI cancer | 1.3% | 1.3% |
| Renal Effects | | |
| Serious adverse events of renal failure | 1.1% | 1.5% |
| eGFR Change from baseline treatment difference (ml/min/1.73m$^2$)<br>End of treatment (n=14820)<br>1 month after treatment end (n=2650) | <br><br>-2.5 (-3.0, -2.1)<br>-0.1 (-1.4, 1.1) | |

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# Darapladib Side Effects Leading to Study Drug Discontinuation

| Diarrhea & Odor Adverse Events | Placebo (N=7890) | | Darapladib (N=7912) | |
|---|---|---|---|---|
| | n (%) | Rate per 100 PY | n (%) | Rate per 100 PY |
| Diarrhea | 60 (0.8%) | 0.21 | 254 (3%) | 0.92 |
| Abnormal feces | 5 (<0.1%) | 0.02 | 177 (2%) | 0.64 |
| Abnormal skin odor | 4 (<0.1%) | 0.01 | 174 (2%) | 0.63 |
| Abnormal urine odor | 1 (<0.1%) | <0.01 | 113 (1%) | 0.40 |

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

# Implications

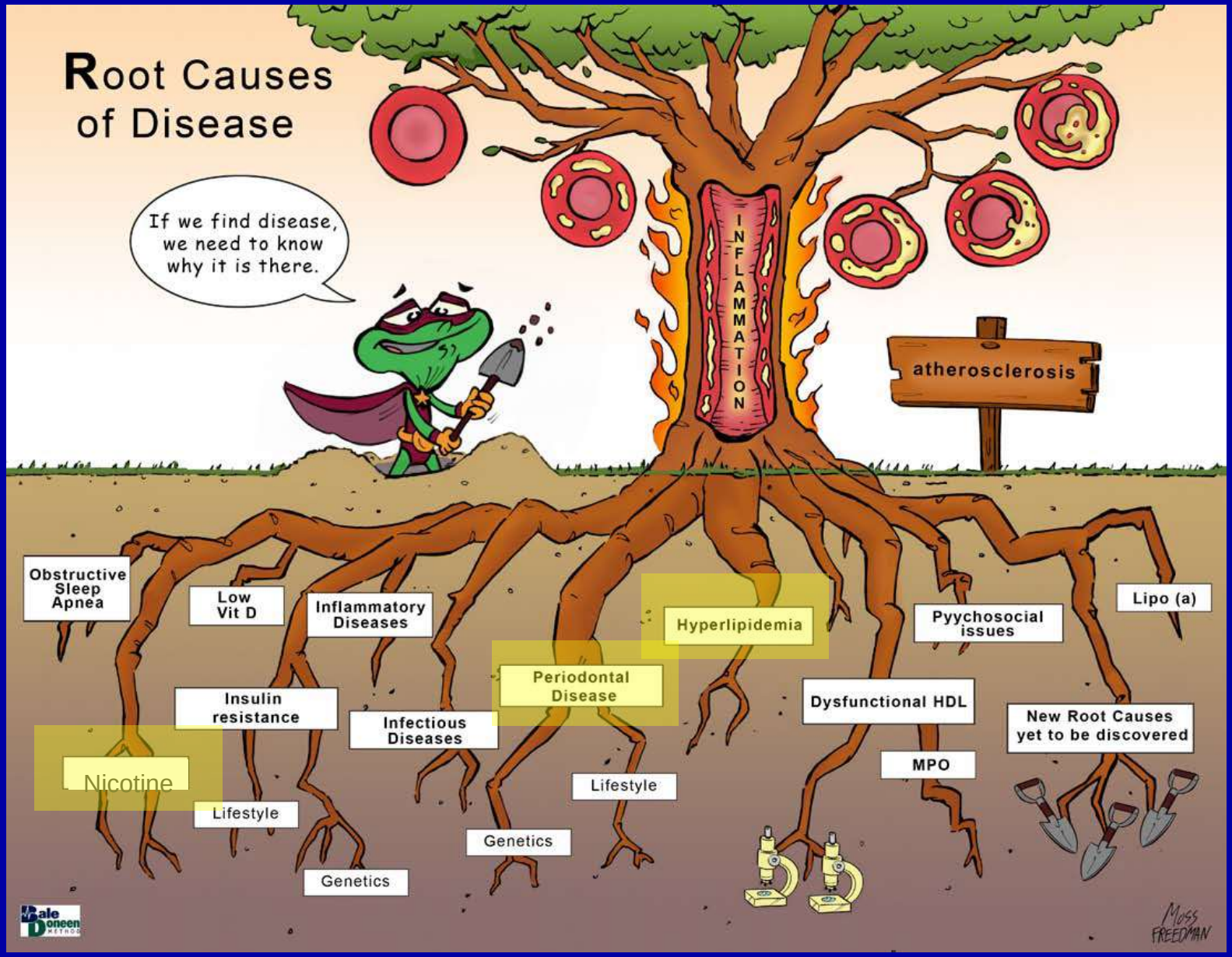
The STABILITY trial is the first large scale randomized global trial to test a novel mechanism of inhibition of inflammation in the atherosclerotic plaque; (to see benefit there would need to be inflammation. *)

Further analyses of the trial results based on biomarkers and genetics will explore if darapladib might be useful in specific patient subsets

No Lp-PLA2 levels reported in trial!!!

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. (2014). New England Journal of Medicine, 140330050005008. doi: 10.1056/NEJMoa1315878

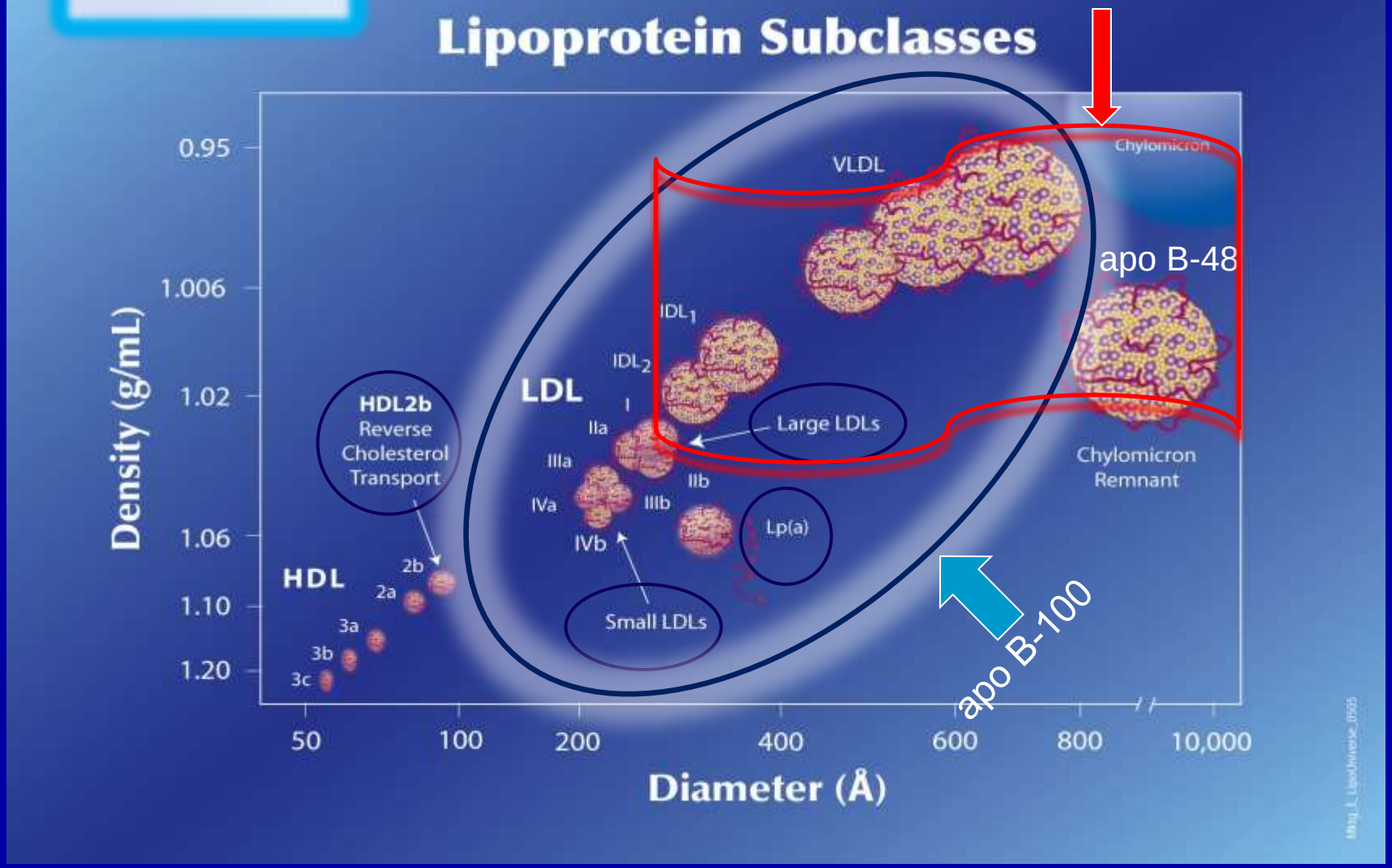
* BDM thoughts



Gross overview

# This is not enough!!!!

Remnant cholesterol




all contain cholesterol and cholesterol esters; lower the density- higher amount cholesterol

# Lipidomics via Mass Spectrometry can Improve CV Risk Assessment

- 685 pts; prospective 10 yr. study; baseline samples evaluated for predicting CV event risk; 90 CV events.

- Mass spectrometry (MS) is the preferred method for in-depth studies of lipid-related pathomechanisms.

- 8 different lipid classes: phosphatidylcholine (PC), lysophosphatidylcholine (LPC), cholesterol ester (CE), sphingomyelin (SM), phosphatidylserine (PS), phosphatidylethanolamine (PE), lysophosphatidylethanolamine (LPE), and triacylglycerol (TAG).

Stegemann, C., et. al. (2014). Lipidomics Profiling and Risk of Cardiovascular Disease in the Prospective Population-Based Bruneck Study. *Circulation*. Volume 129(18):1821-1831

# Lipidomics via Mass Spectrometry can Improve CV Risk Assessment

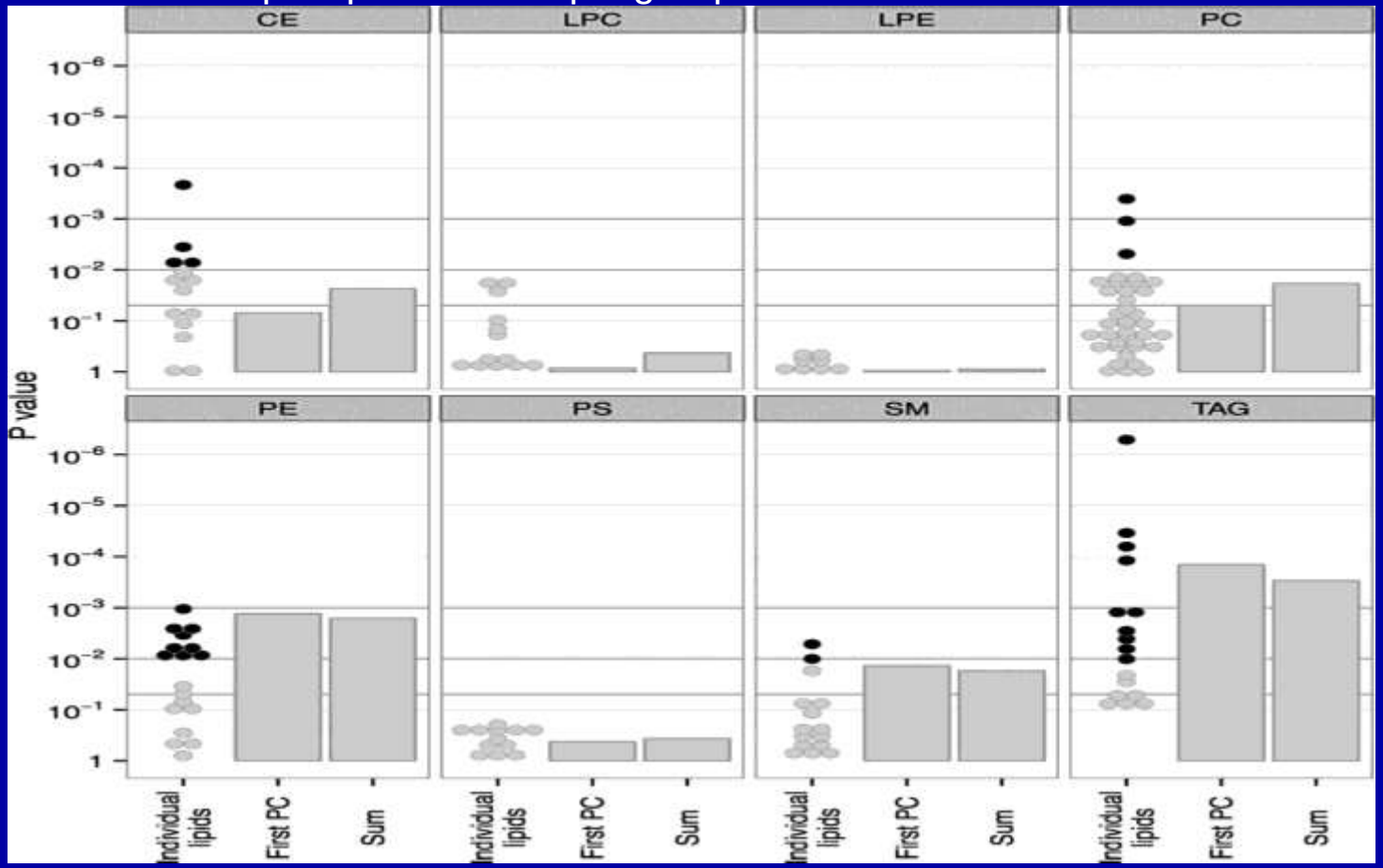
- 135 lipid species attributable to the 8 different lipid classes.

- 28 species for six of the classes (TAGs, CEs, PEs, PCs, LPCs, and SMs) were significantly associated with risk.

Stegemann, C., et. al. (2014). Lipidomics Profiling and Risk of Cardiovascular Disease in the Prospective Population-Based Bruneck Study. *Circulation*. Volume 129(18):1821-1831

# Lipidomics for CV Risk Assessment

Manhattan plot depicting significance levels (logarithmic y axis) for assoc. of individual lipid species and lipid groups with incident CVD.




broad diversity of potential CV effects of lipid species within most lipid classes.
individual lipids outperform lipid summary measures for CV risk assessment

**Stegemann C et al. Circulation. 2014;129:1821-1831**

# Lipidomics via Mass Spectrometry can Improve CV Risk Assessment

- 3 lipid species TAG(54:2), CE(16:1), and PE(36:5) were most consistently related to incident CVD.
- Proportions associated with CVD were 30% for CE(16:1), 61% for TAG(54:2), and 83% for PE(36:5).

Stegemann, C., et. al. (2014). Lipidomics Profiling and Risk of Cardiovascular Disease in the Prospective Population-Based Bruneck Study. *Circulation*. Volume 129(18):1821-1831

# Lipidomics Improve CV Risk Assessment

Study challenges the current practice of lipid management focused on drug rx of cholesterol rather than dietary rx to effect lipid composition.

Need to establish novel lipid biomarkers and therapeutic targets beyond the traditional lipid measurements.

Stegemann C et al. Circulation. 2014;129:1821-1831

# PD Associated with Pre-diabetes (IGT)

- 1,165 non-DM; 51% female; 30-80 yo; full-mouth periodontal exam and an OGTT

- PD = a) none/mild; moderate; severe

  b) 75$^{th}$ percentile if mean probing depth ≥2.19 mm or attachment loss≥1.78 mm

- Abnormal OGTT, if FBG ≥100mg/dL (IFG) or 2 hr. glucose ≥140mg/dL (IGT)

Arora, N., et. al. (2014). Periodontal Infection, Impaired Fasting Glucose and Impaired Glucose Tolerance: Results from The Continuous National Health and Nutrition Examination Survey 2009-2010. *J Clin Periodontol*. doi: 10.1111/jcpe.12258

# PD Associated with Pre-diabetes (IGT)

Prevalence: 57% N/Mild; 33% M; 10% S; IGT-16%

Significant increased risk of IGT with severe PD & with 75$^{th}$ percentile compared to none/mild

OR- 1.93 (95% CI- 1.18-3.17) P=0.02

OR - 2.05 (95% CI- 1.24-3.39) P=0.005

Respectively

Adjusted for: age, sex, smoking, calories, alcohol, exercise, BMI, race/ethnicity, education level.

Arora, N., et. al. (2014). *J Clin Periodontol*. doi: 10.1111/jcpe.12258

# PD Associated with Pre-diabetes

PD was not related to IFG

IFG does not predict new onset diabetes when the 2hr. glucose is <140mg/dL*

Arora, N., et. al. (2014). *J Clin Periodontol*. doi: 10.1111/jcpe.12258

*Abdul-Ghani, et. al. (2010). Minimal contribution of fasting hyperglycemia to the incidence of type 2 diabetes in subjects with normal 2-h plasma glucose. *Diabetes Care, 33*(3), 557-561. doi: 10.2337/dc09-1145

# PD Influences CRP in Stable Post-MI Pts

- 93 CAD (55% post-MI) pts.; 40% female; 63 yo ± 10 yrs.
- PD determined by two calibrated periodontists in six sites per tooth at all teeth; serum CRP levels.
- Association btw PD and CRP adjusted for: sex, BMI, A1c, smoking and oral hypoglycemic meds.

Flores, M. F., et. al. (2014). Periodontal status affects C-reactive protein and lipids in patients with stable heart disease from a tertiary care cardiovascular clinic. *J Periodontol, 85*(4), 545-553.

# PD Influences CRP in Stable Post-MI Pts

Severe periodontitis defined as at least two interproximal sites with AL ≥6 mm and one or more interproximal sites with PD ≥5 mm in non-adjacent teeth.

Flores, M. F., et. al. (2014). Periodontal status affects C-reactive protein and lipids in patients with stable heart disease from a tertiary care cardiovascular clinic. *J Periodontol, 85*(4), 545-553.

# PD Influences CRP in Stable Post-MI Pts

Pts without MI hx: no significant difference in CRP with and without PD.

Pts with MI hx: significant association btw CRP and severe periodontitis in the multivariable model:

p=0.008

Flores, M. F., et. al. (2014). Periodontal status affects C-reactive protein and lipids in patients with stable heart disease from a tertiary care cardiovascular clinic. *J Periodontol, 85*(4), 545-553.

# BDM Thoughts

Too bad they did not measure better indicators of ‘arterial’ inflammation such as: Lp-PLA2, MPO and MACR.

# PD Treatment Reduces Healthcare Costs

- Study to investigate whether or not PD rx impacts overall healthcare costs.
- Data base-1.6 million pts with both United Concordia Dental Care and Highmark Medical Care; five-year period ‘05-’09.
- Clients decided to either receive or not receive PD treatment.

Jeffcoat, M., et. al., Periodontal Therapy Improves Outcomes in Systemic Conditions, Abstract, *American Association of Dental Research*, March 21, 2014

# PD Treatment Reduces Healthcare Costs

- PD rx was mainly scaling and root planning; few flap surgeries; maintenance was annual cleaning.
- Healthcare costs: physician visits; hospital admissions; pharmacy costs.
- Looking for an association, but with the large numbers involved there is an inference of causality.

Jeffcoat, M., et. al., Periodontal Therapy Improves Outcomes in Systemic Conditions, Abstract, *American Association of Dental Research*, March 21, 2014

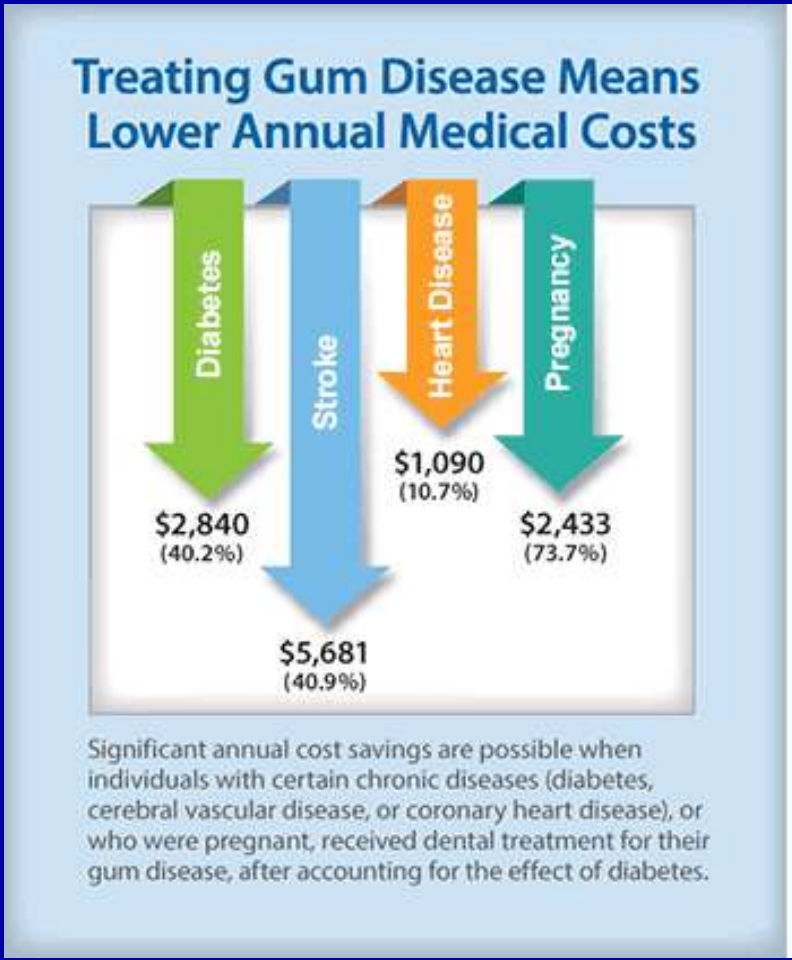
# PD Treatment Reduces Healthcare Costs

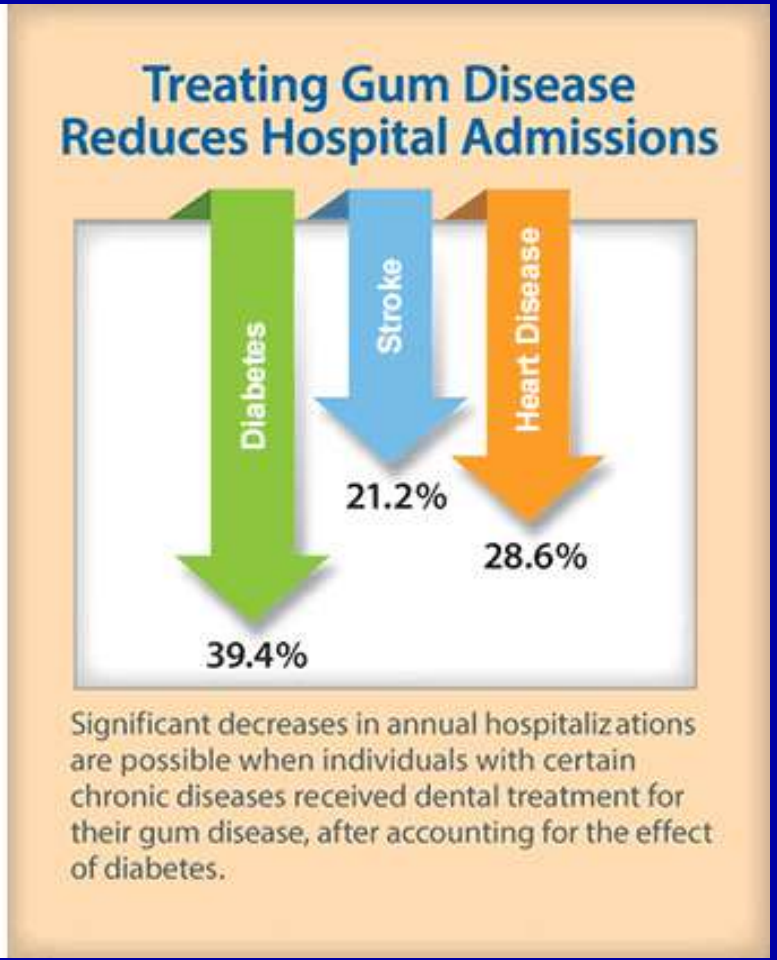
338,891 PD pts with one or more of the following type 2 DM, CAD, CVD and/or pregnant; insurance records for review from ‘05-’09; rx’ed or un-rx’ed.

Due for publication in: *American Journal of Preventive Medicine* late summer of 2014.

Jeffcoat, M., et. al., Periodontal Therapy Improves Outcomes in Systemic Conditions, Abstract, *American Association of Dental Research*, March 21, 2014

# PD Treatment Reduces Healthcare Costs




Jeffcoat, M., et. al., Periodontal Therapy Improves Outcomes in Systemic Conditions, Abstract, *American Association of Dental Research*, March 21, 2014

# PD Treatment Reduces Healthcare Costs

- Results support the evidence of the oral-systemic connection.
- Indicates a need to increase the healthcare dollars spent on dental care. (30%-hospital care, 22% physician, 11%- meds, 4% dentistry)
- There needs to be a merger of medical and dental health insurance.

Jeffcoat, M., et. al., Periodontal Therapy Improves Outcomes in Systemic Conditions, Abstract, *American Association of Dental Research*, March 21, 2014
Jeffcoat, M., HIGHMARK, INC. Teleconference. Moderator: Leilyn Perri
03-26-12/9:00 a.m. ET

# Oh My!!!

# Electronic Cigarettes (e-cigarettes)

- Patented in 2004 they were designed to mimic the look and feel of conventional cigarettes, creating a smoke-free vapor (with or without nicotine) that is inhaled by the user.
- They are not subject to regular smoking laws and can be used in nonsmoking areas.
- FDA permits them to be sold as tobacco products and does not allow marketing for smoking cessation.

Franck, C., et. al. (2014). Electronic Cigarettes in North America: History, Use, and Implications for Smoking Cessation. *Circulation, 129*(19), 1945-1952.

# Electronic Cigarettes (e-cigarettes)

- Two types: disposable & rechargeable.
- Available in several flavors, including tobacco, menthol, chocolate, vanilla, and various fruit flavors.
- Cartridges vary in strengths of nicotine content, including nicotine free.
- Cheaper than cigarettes.

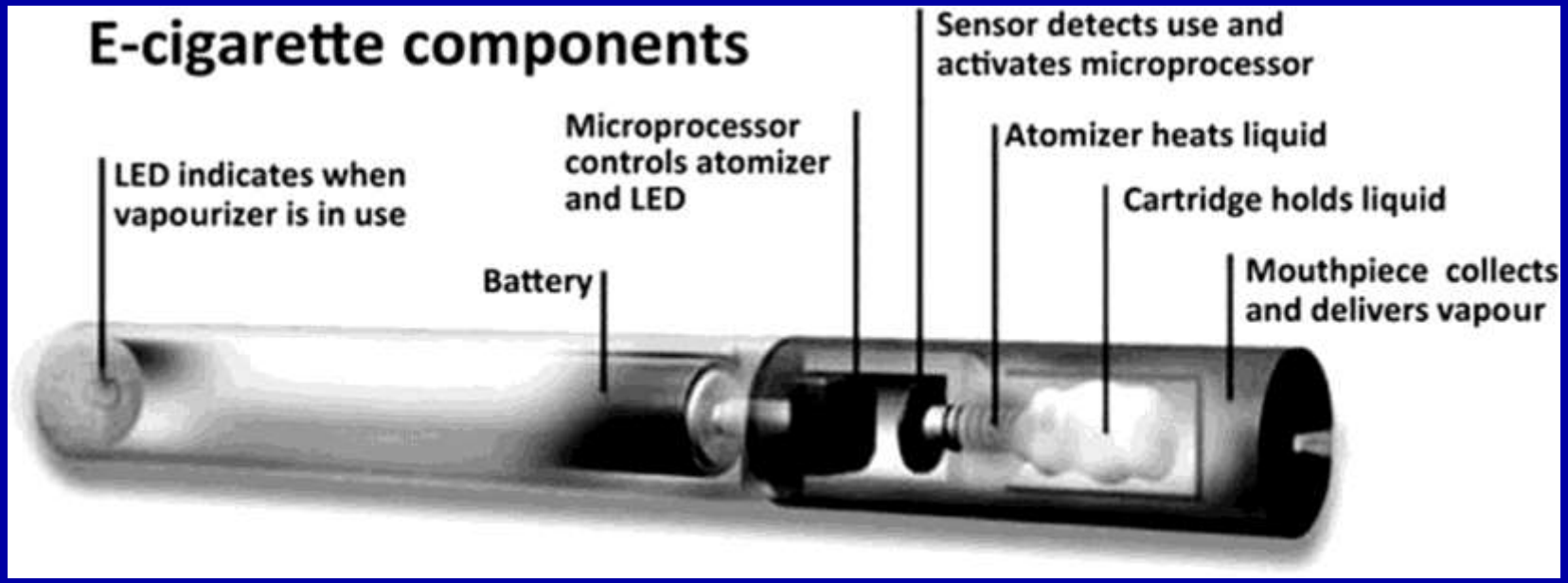
Franck, C., et. al. (2014). Electronic Cigarettes in North America: History, Use, and Implications for Smoking Cessation. *Circulation, 129*(19), 1945-1952.

# Electronic Cigarettes (e-cigarettes)

- The liquid solution of e-cigarettes is propylene glycol, with or without nicotine.
- Vaporizing the solution produces a smoke-like aerosol that is subsequently inhaled.
- Believed to be a safer than cigarettes by eliminating the inhalation of harmful compounds, including tar and carbon monoxide.

Franck, C., et. al. (2014). Electronic Cigarettes in North America: History, Use, and Implications for Smoking Cessation. *Circulation, 129*(19), 1945-1952.

# Electronic cigarette components.




Franck C et al. Circulation. 2014;129:1945-1952

# Examples of different electronic cigarette (e-cigarette) products.

| Product | Description | Some Brands |
|---|---|---|
| **Disposable e-cigarette**  | Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah. | NJOY OneJoy, Aer Disposable, Flavorvapes |
| **Rechargeable e-cigarette**  | Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively. | Blu, GreenSmoke, EonSmoke |
| **Pen-style, medium-sized rechargeable e-cigarette**  | Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs. | Vapor King Storm, Totally Wicked Tornado |
| **Tank-style, large-sized rechargeable e-cigarette**  | Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified. | Volcano Lavatube |

Grana R et al. Circulation. 2014;129:1972-1986

# Electronic Cigarettes (e-cigarettes): Potential Harm

- Examined vapours from 12 models of e-cigarettes; Nicorette inhalator was used as a reference.
- Formaldehyde and acetaldehyde detected: formaldehyde is carcinogenic & acetaldehyde is possibly carcinogenic.
- Acrolein found which irritates nasal cavity, damages the lungs and may contribute to CVD.
- Traces of the carcinogenic nitrosamines NNN and NNK were also found.

Goniewicz, M. L., et. Al. (2014). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control, 23*(2), 133-139

# Electronic Cigarettes (e-cigarettes): Potential Harm

- Volatile organic chemicals toluene and m, p-xylene were detected; they are carcinogenic, haematotoxic, neurotoxic, and an irritant.

- Toxic metals, cadmium, nickel and lead were found, but were also present in Nicorette inhaler.

Goniewicz, M. L., et. Al. (2014). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control, 23*(2), 133-139

# Electronic Cigarettes (e-cigarettes): Potential Harm

**Table 4** Comparison of toxins levels between conventional and electronic cigarettes

| Toxic compound | Conventional cigarette (μg in mainstream smoke) [35] | Electronic cigarette (μg per 15 puffs) | Average ratio (conventional vs electronic cigarette) |
|---|---|---|---|
| Formaldehyde | 1.6–52 | 0.20–5.61 | 9 |
| Acetaldehyde | 52–140 | 0.11–1.36 | 450 |
| Acrolein | 2.4–62 | 0.07–4.19 | 15 |
| Toluene | 8.3–70 | 0.02–0.63 | 120 |
| NNN | 0.005–0.19 | 0.00008–0.00043 | 380 |
| NNK | 0.012–0.11 | 0.00011–0.00283 | 40 |

NNK, N′-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine.

Goniewicz, M. L., et. Al. (2014). Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control, 23*(2), 133-139

# Electronic Cigarettes (e-cigarettes): Potential Harm

One puff with the highest nicotine content contains 20% of the nicotine contained in a puff of a cigarette.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): Marketing

- Most popular: healthier (95%), cheaper (93%), cleaner (95%), can be smoked anywhere (88%), circumvent smoke-free policies (71%); no secondhand smoke (76%) and modern (73%).
- Celebrity endorsements.
- Cessation-related claims -66%
- Health claims by doctors – 22%.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): Marketing

E-cigarette advertising on television and radio is mass marketing of an addictive nicotine product for use in a recreational manner to new generations who have never experienced such marketing.

Cigarette companies have been unable to market their products on television and radio since the 1970s.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): TV Marketing

- 519 Florida adult smokers; surveyed after seeing TV ad for e-cigarettes.
- Ad elicited urge to smoke cigarettes (75.8%), as well as urge to quit cigarettes (74.6%).
- Thought the ads were made for people like them (88.6%) and they would try e-cigarettes in the future (66.0%).

Kim, A. E., Lee, Y. O., Shafer, P., Nonnemaker, J., & Makarenko, O. (2013). Adult smokers' receptivity to a television advert for electronic nicotine delivery systems. *Tob Control*. doi: 10.1136/tobaccocontrol-2013-051130

# Electronic Cigarettes (e-cigarettes): Marketing

Among US adolescents e-cigarette use rose from 3.3% in 2011 to 6.8% in 2012.

Dual use with cigarettes: 61% in US middle school students and 80% among US high school students in 2011.

Rapid market penetration of e-cigarettes among youth!

Some youth are initiating use of nicotine, an addictive drug, with e-cigarettes!!!

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): Potential Harm

Evidence to date from clinical trials does not demonstrate that e-cigarettes are efficacious for cessation.

Dual use could decrease # cigarettes smoked, but in terms of cancer the data suggest that lung cancer mortality increases more with additional yrs of smoking than additional cigarettes per day.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): Patient Information

- They are unregulated, contain toxic chemicals, and have not been proven as cessation devices.
- Should not use indoors or around children.
- There are no long-term safety studies.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes): Patient Information

Data reviewed in this article, together with evidence of dual use and youth initiation of e-cigarette use, do not demonstrate any hypothesized harm-reducing effect.

As of March 2014, 27 states had laws restricting sales to minors and 3 states (New Jersey, North Dakota, and Utah) and >100 municipalities prohibit the use of e-cigarettes in 100% smoke- free indoor environments.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes)

- Nicotine e-cigarettes are not currently authorized for sale in Canada.
- Britain has recently determined that e-cigarettes will be licensed as medication beginning in 2016.
- New Zealand, Denmark, and Austria classify them as medication.
- Brazil, Norway, and Singapore ban them from sale entirely.

Franck, C., et. al. (2014). Electronic Cigarettes in North America: History, Use, and Implications for Smoking Cessation. *Circulation, 129*(19), 1945-1952.

# Electronic Cigarettes (e-cigarettes): Patient Information

E-cigarette emissions are not merely “harmless water vapor” !

E-cigarettes can be a source of indoor air pollution.

E-cigarettes undermine the benefits of smoke-free policies.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-Cigarettes: A Scientific Review. *Circulation, 129*(19), 1972-1986.

# Electronic Cigarettes (e-cigarettes)

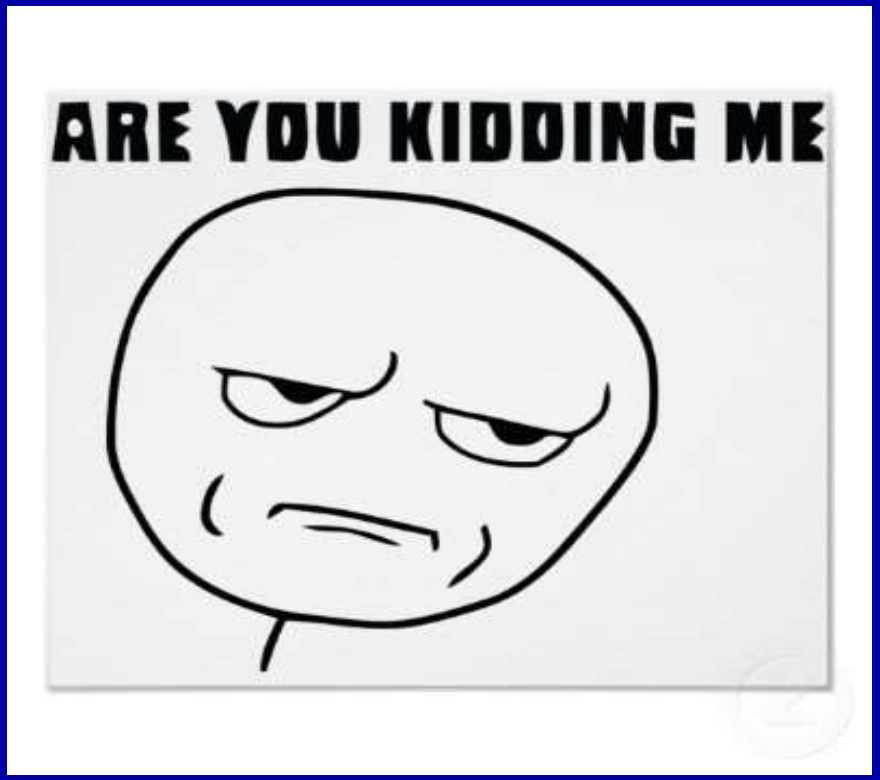
- There is a lack of data concerning the safety and efficacy.

- Ethical concerns with use in minors (gateway to cigarette smoking) and the potential to undermine efforts to reduce cigarette smoking.

Franck, C., et. al. (2014). Electronic Cigarettes in North America: History, Use, and Implications for Smoking Cessation. *Circulation, 129*(19), 1945-1952.


Dr. Richard Carmona addresses students at the Arnold School of Public Health during his appearance on campus Aug. 21.

2008, campaigning against tobacco!




# Former U.S. Surgeon General Richard Carmona joined Board of Directors of NJOY (leading e-cigarette company).

Stipulations:

Request FDA regulation.

Conduct and publish research in peer-reviewed journals.

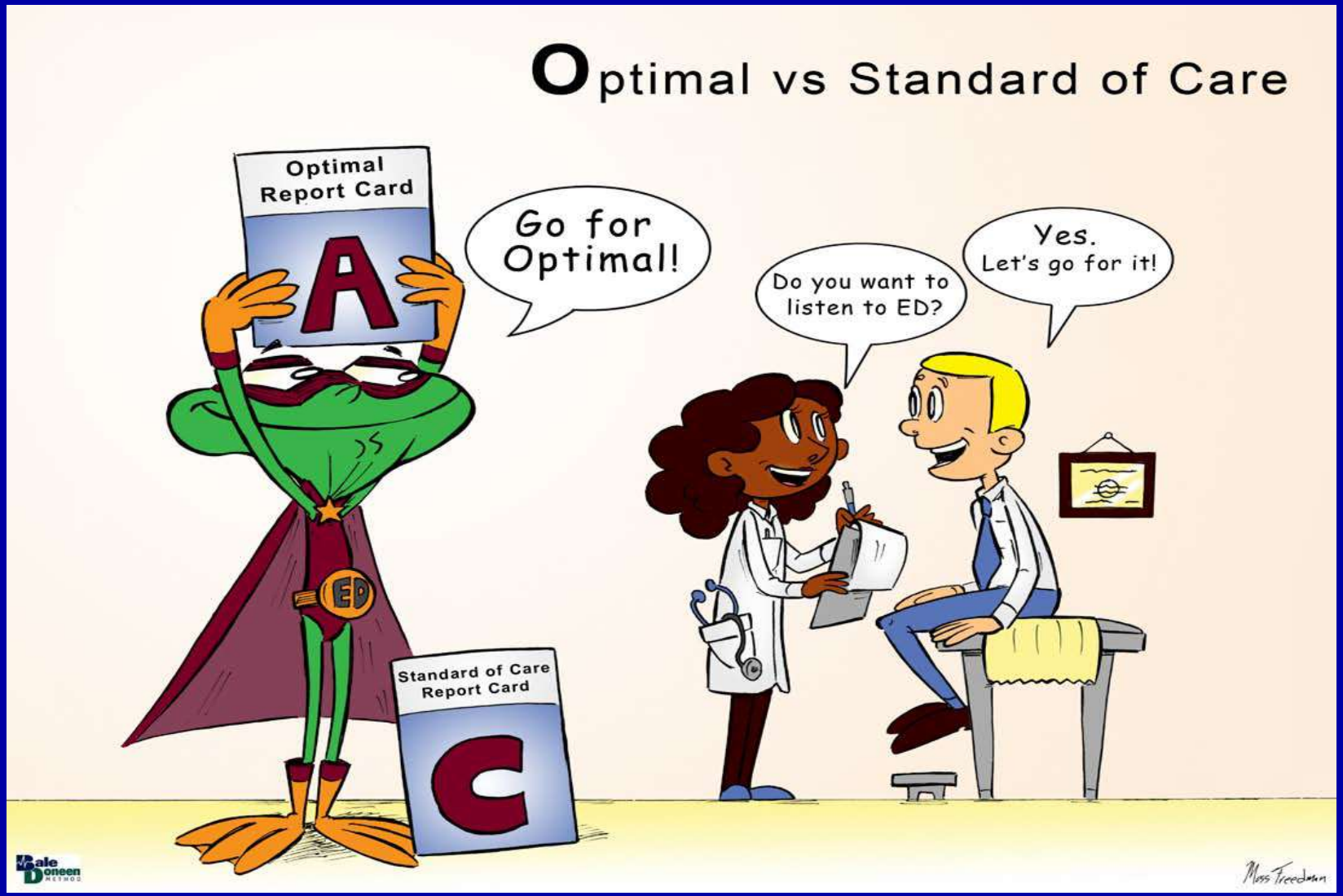
Don't use my name in advertising.

Don't market to kids.

"abstinence has failed --- we have to take advantage of every opportunity with a reasonable prospect for harm reduction."

Schmidt, C. (2014). A Former Surgeon General Lends His Support to E-Cigarettes. *Science, 343*(6171), 589.

# Optimal Care



# NT pro-BNP is Independent Predictor of Stroke

- 30,239 black & white pts; baseline NT-proBNP measured in 1,402 pts.; during 5.4 yrs 546 pts suffered an ischemic stroke.

- Evaluated quartiles of NT-proBNP as predictor of stroke.

Cushman, M., et., al. (2014). N-Terminal Pro-B-type Natriuretic Peptide and Stroke Risk: The Reasons for Geographic and Racial Differences in Stroke Cohort. *Stroke*. doi: 10.1161/STROKEAHA.114.004712

# NT pro-BNP is Independent Predictor of Stroke

Greatest association was with cardioembolic stroke, highest vs lowest quartile

HR-9.1 (95% CI, 2.9–29.2)

Adjusted for: age, race, sex, income, education, traditional stroke risk factors, renal function

No change after eliminating pts with baseline HF and or AF

Cushman, M., et., al. (2014). N-Terminal Pro-B-type Natriuretic Peptide and Stroke Risk: The Reasons for Geographic and Racial Differences in Stroke Cohort. *Stroke*. doi: 10.1161/STROKEAHA.114.004712

# NT pro-BNP is Independent Predictor of Stroke

**Table 3. Hazard Ratio (95% Confidence Interval) of Ischemic Stroke by Baseline NT-ProBNP***

| | NT-ProBNP Quartiles† | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | *P* for Trend |
| All ischemic stroke, n | 60 | 82 | 110 | 294 | |
| Model 1 of cohort | Reference | 1.3 (0.9–1.9) | 1.7 (1.1–2.5) | 3.9 (2.6–5.8) | <0.001 |
| Model 2 | Reference | 1.1 (0.7–1.7) | 1.3 (0.8–2.0) | 2.9 (1.9–4.5) | <0.001 |
| Model 3 | Reference | 1.1 (0.7–1.9) | 1.2 (0.8–1.9) | 2.9 (1.8–4.5) | <0.001 |
| Small vessel stroke, n | 8 | 10 | 2 | 47 | |
| Model 2 | Reference | 2.2 (0.97–5.1) | 1.7 (0.7–5.3) | 2.8 (0.99–5.3) | 0.17 |
| Large vessel stroke, n | 12 | 7 | 24 | 47 | |
| Model 2 | Reference | 1.0 (0.3–3.0) | 1.5 (0.5–4.4) | 3.5 (1.3–9.0) | 0.02 |
| Cardioembolic stroke, n | 5 | 9 | 18 | 110 | |
| Model 2 | Reference | 1.2 (0.3–4.7) | 1.8 (0.5–6.4) | 9.1 (2.9–28.2) | <0.001 |
| Unclassified stroke, n | 34 | 43 | 53 | 124 | |
| Model 2 | Reference | 1.1 (0.6–1.9) | 1.0 (0.6, 1.8) | 2.1 (1.2, 3.8) | 0.01 |

*Model 1 adjusted for age, race, age–race interaction, and sex. Model 2 added income, education, smoking, hypertension medication use, systolic blood pressure, atrial fibrillation, left ventricular hypertrophy, diabetes mellitus, and prevalent heart disease. Model 3 added estimated glomerular filtration rate, albuminuria, and heart failure. NT-proBNP indicates N-terminal pro–B-type natriuretic peptide.

†Quartile cut points as in Table 1.

Cushman, M., et., al. (2014). N-Terminal Pro-B-type Natriuretic Peptide and Stroke Risk: The Reasons for Geographic and Racial Differences in Stroke Cohort. *Stroke*. doi: 10.1161/STROKEAHA.114.004712

# NT pro-BNP is Independent Predictor of Stroke

- NT-proBNP improved risk classification for stroke by traditional stroke risk factors for 27%.
- NT-proBNP may be involved in the causal path for stroke, perhaps related to atherosclerosis.
- Study supports the clinical use of NT-proBNP in primary prevention settings.

Cushman, M., et., al. (2014). N-Terminal Pro-B-type Natriuretic Peptide and Stroke Risk: The Reasons for Geographic and Racial Differences in Stroke Cohort. *Stroke*. doi: 10.1161/STROKEAHA.114.004712

# BDM Thoughts

- Obviously, may be an indicator of silent arrhythmias

- May be indicating silent heart attacks (and indirectly silent strokes)

# EDFROG IRA

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

# Keep the Rhythm

# Extra Virgin Olive Oil in a Mediterranean Diet Reduces AF Risk

- PREDIMED study; 6705 pts without AF; randomized Mediterranean diet with extra virgin olive oil (EVOO) or extra nuts and control low fat diet; followed 4.7 yrs.
- EVOO arm EVOO was ≥15% of total energy intake
- New onset AF: 72 EVOO; 82 extra nuts; 92 low fat diet.

Martinez-Gonzalez, M. A., (2014). Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006921

# Extra Virgin Olive Oil in a Mediterranean Diet Reduces AF Risk

Compared to low fat diet the HR for new onset AF was:

EVOO

HR-0.62 (95% CI- 0.45–0.85)

extra nuts

HR-0.89 (95% CI 0.65–1.20)

Martinez-Gonzalez, M. A., (2014). Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006921

# Extra Virgin Olive Oil in a Mediterranean Diet Reduces AF Risk

Superior results with EVOO compared to nuts can be explained by inflammation and oxidation.

Higher content of polyphenols in EVOO have anti-inflammatory and antioxidant properties.

There was a significant reduction in CRP in the EVOO group, but not in the MeDiet+nuts group.

Martinez-Gonzalez, M. A., (2014). Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006921

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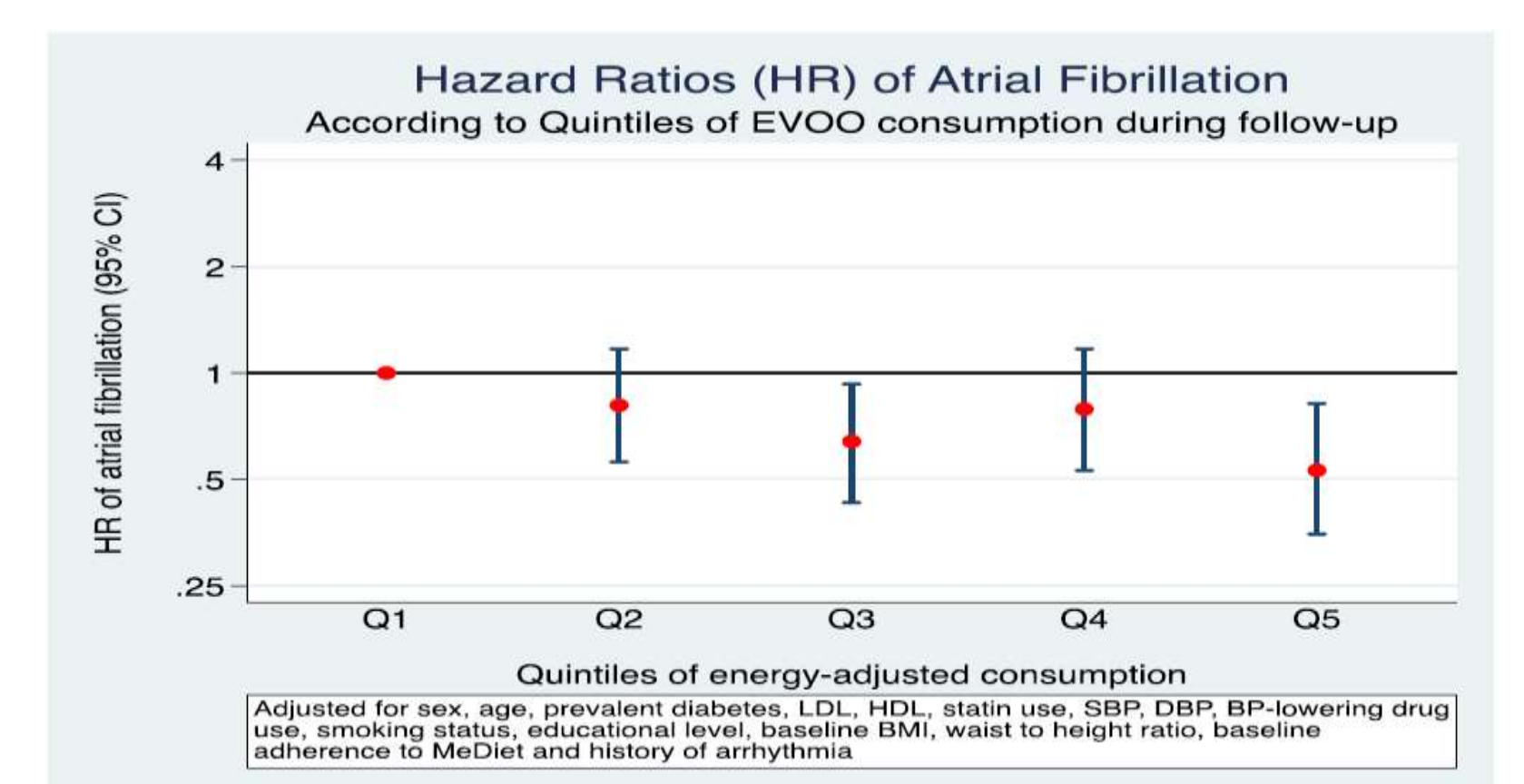


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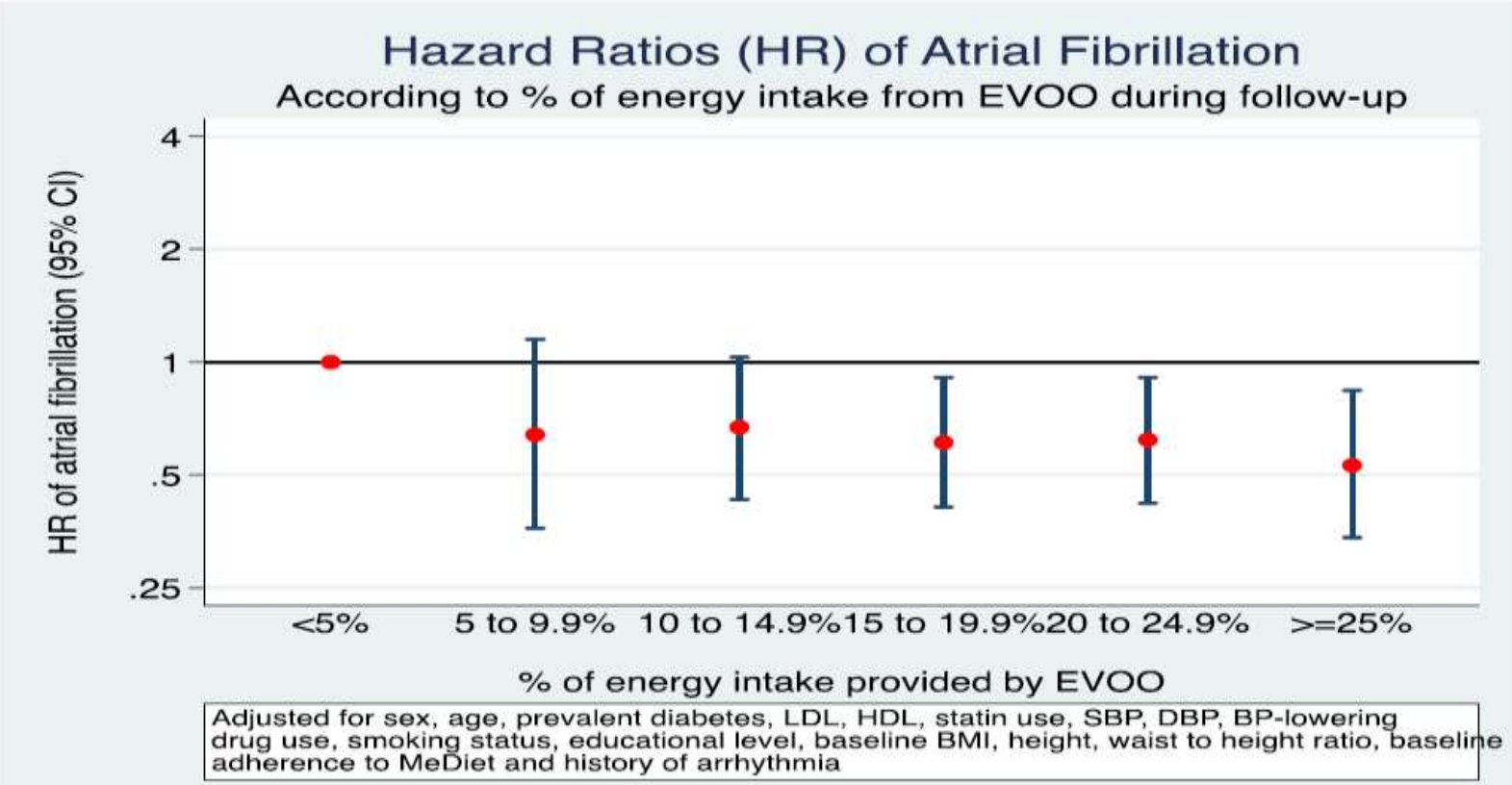



Martinez-Gonzalez, M. A., (2014). Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006921

# BDM Thoughts

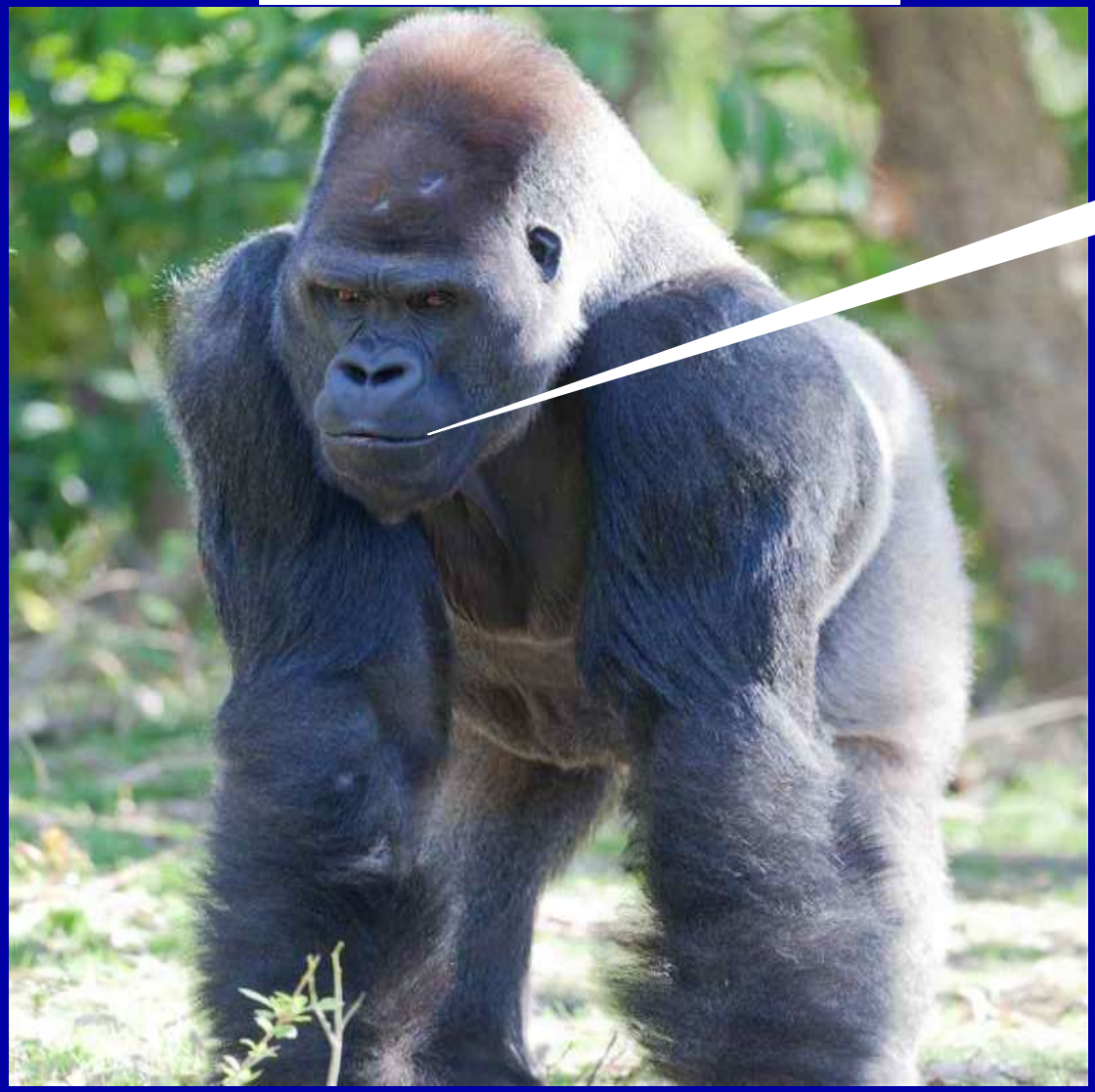
With lifetime risk of AF being ~25%, we should seek out receipts with EVOO.

If you are apoE 4, this may not be good advice.

Martinez-Gonzalez, M. A., (2014). Extra-Virgin Olive Oil Consumption Reduces Risk of Atrial Fibrillation: The PREDIMED Trial. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006921

# New Player in Cholesterol Therapy!

## Evolocumab



# PCSK9 (proprotein convertase subtilisin/kexin type 9) Basic Science

- PCSK9 regulates serum LDL by interacting with the LDL receptor (LDLR).
- PCSK9 modulates LDL by posttranslational downregulation of hepatic LDLR.
- The PCSK9:LDLR complex is endocytosed and directed to the endosome/lysosome compartment for degradation. = reduction in # LDLR = higher serum LDL.

Chan, J. C., et. al. (2009). A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci U S A, 106*(24), 9820-9825.

# PCSK9 (proprotein convertase subtilisin/kexin type 9) Basic Science

- Hypothesized that attenuation of statin-mediated cholesterol-lowering effect is due to causing an increase in PCSK9 levels.
- Theoretically a monoclonal antibody to PCSK9 would produce an increase in LDLRs and decrease LDL.
- This antibody should enhance the statin-mediated LDL lowering effect, as well.

Chan, J. C., et. al. (2009). A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci U S A, 106*(24), 9820-9825.

# PCSK9 (proprotein convertase subtilisin/kexin type 9) Basic Science

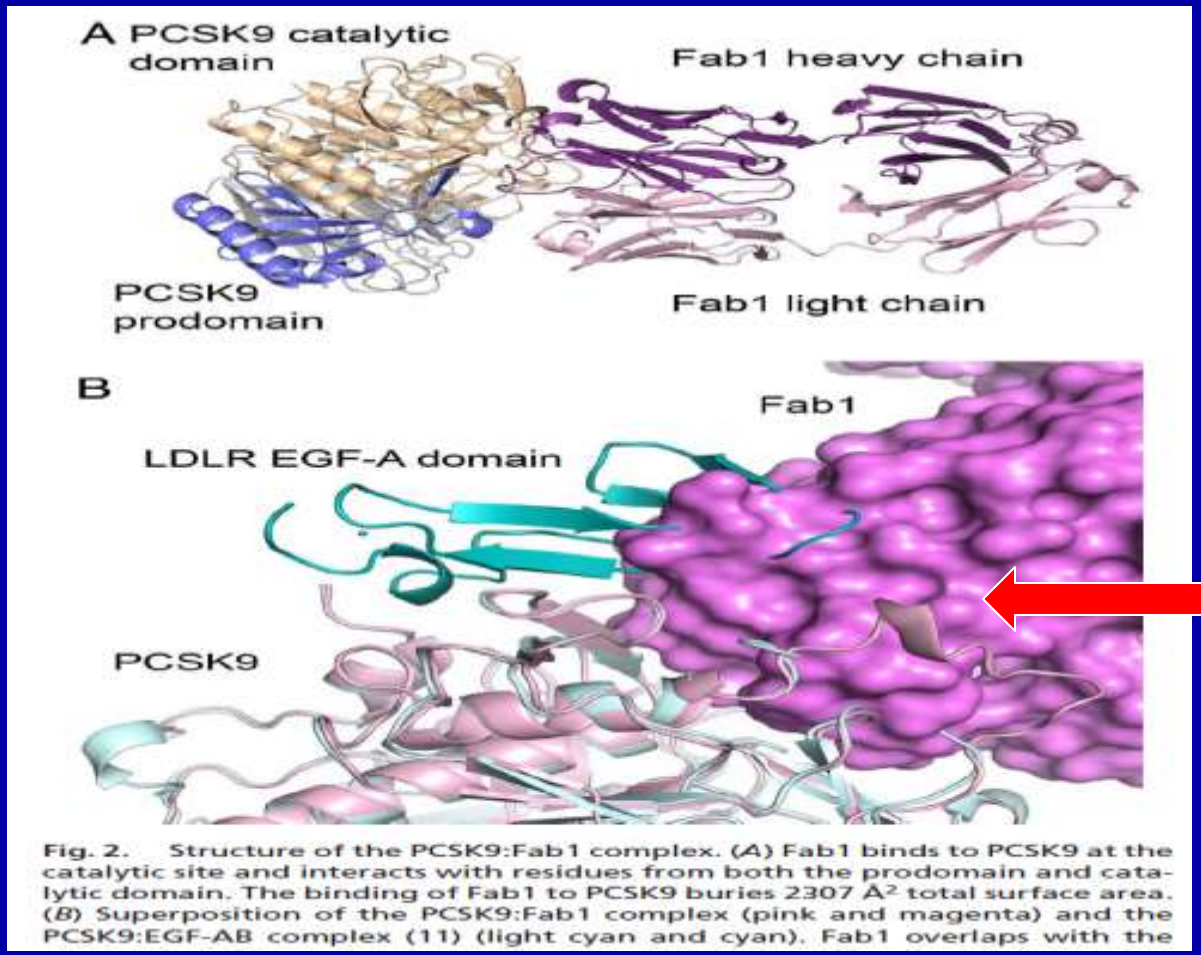



Fig. 2. Structure of the PCSK9:Fab1 complex. (*A*) Fab1 binds to PCSK9 at the catalytic site and interacts with residues from both the prodomain and catalytic domain. The binding of Fab1 to PCSK9 buries 2307 Å$^2$ total surface area. (*B*) Superposition of the PCSK9:Fab1 complex (pink and magenta) and the PCSK9:EGF-AB complex (11) (light cyan and cyan). Fab1 overlaps with the

Fab1 is part of the monoclonal antibody

numerous hydrogenbond and hydrophobic interactions with PCSK9

Chan, J. C., et. al. (2009). *Proc Natl Acad Sci U S A, 106*(24), 9820-9825.

# PCSK9 (proprotein convertase subtilisin/kexin type 9) Basic Science

- Antibody modality is a novel approach for rx of hypercholesterolemia that may prove superior to statins.

- An antibody approach may complement statin rx for cases in which statin rx alone achieves suboptimal results.

Chan, J. C., et. al. (2009). *Proc Natl Acad Sci U S A, 106*(24), 9820-9825.

# PCSK9 Antibody (AMG 145) Shows Success

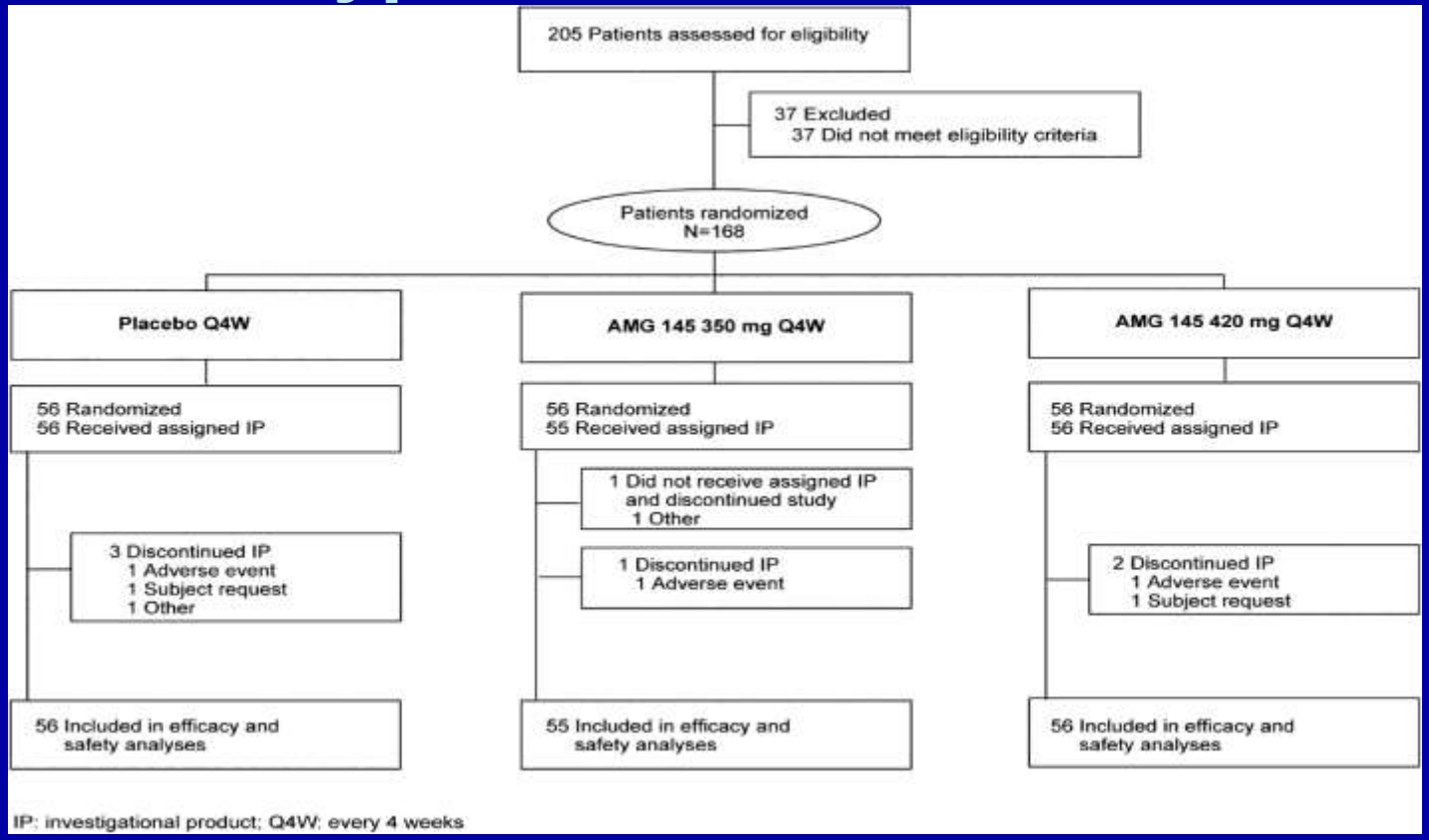
- 406 pts; were assigned to AMG 145 70 mg (n=45), 105 mg (n=46), or 140 mg (n=45) every 2 wks; AMG 145 280 mg (n=45), 350 mg (n=45), or 420 mg (n=45) every 4 wks; placebo every 2 wks (n=45) or every 4 wks (n=45); or ezetimibe (n=45). 3 month trial.

- Q 2 wks rx lowered LDL: 41.0%; 43.9%; 50.9%
- Q 4 wks rx lowered LDL: 39.0%; 43.2%; 48.0%
- Ezetimibe lowered LDL: 14.7%

- No deaths of serious adverse side effects reported

Koren, M. J., et. al. (2012). Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *The Lancet, 380*(9858), 1995-2006.

# AMG 145 Effective in Heterozygous Familial Hypercholesterolemia

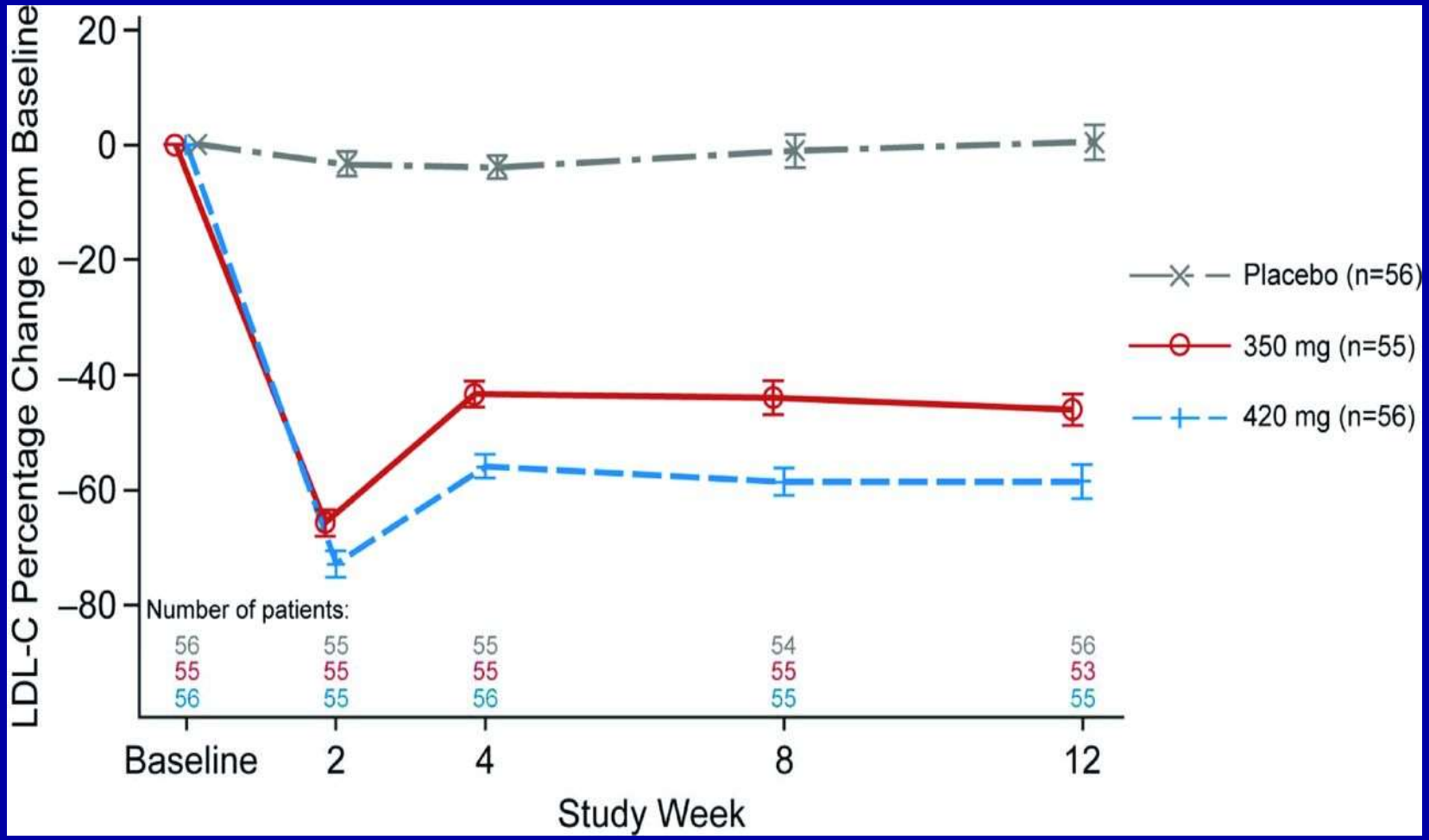



Q 4 wk

Raal, F., et. al. (2012). Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia: The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial. *Circulation, 126*(20), 2408-2417.

# AMG 145 Effective in Heterozygous Familial Hypercholesterolemia

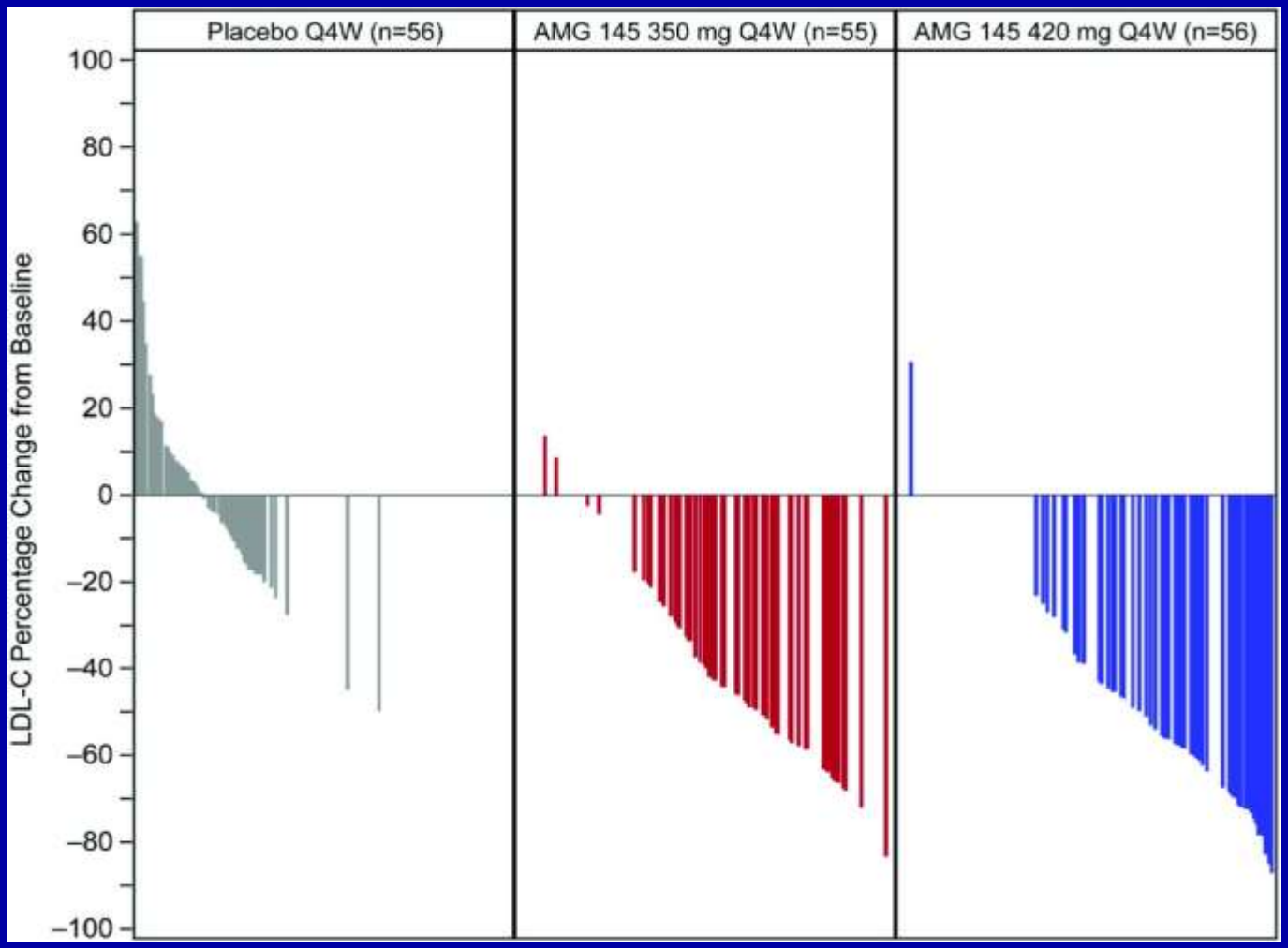
% change from baseline in calculated LDL-C to week 12.




Raal F et al. Circulation 2012;126:2408-2417

# AMG 145 Effective in Heterozygous Familial Hypercholesterolemia

Individual pt % change from baseline in LDL




Raal F et al. Circulation 2012;126:2408-2417

# Evolocumab Lowers Lipo (a)

- Pooled analysis 1,359 pts in 4 phase II trials; rx'ed 12 wks.
- 140 mg q 2 wks reduced lipo (a) 29.5% (23.3% to 35.7%).
- 420 mg q 4 wks reduced lipo (a) 24.5% (20.4% to 28.7%)
- Reductions significantly correlated with decrease in apo B with an r value of 0.5203 - $p < 0.001$.

Raal, F. J., et. al. (2014). Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): A Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials. *J Am Coll Cardiol, 63*(13), 1278-1288.

# Evolocumab Lowers Lipo (a)

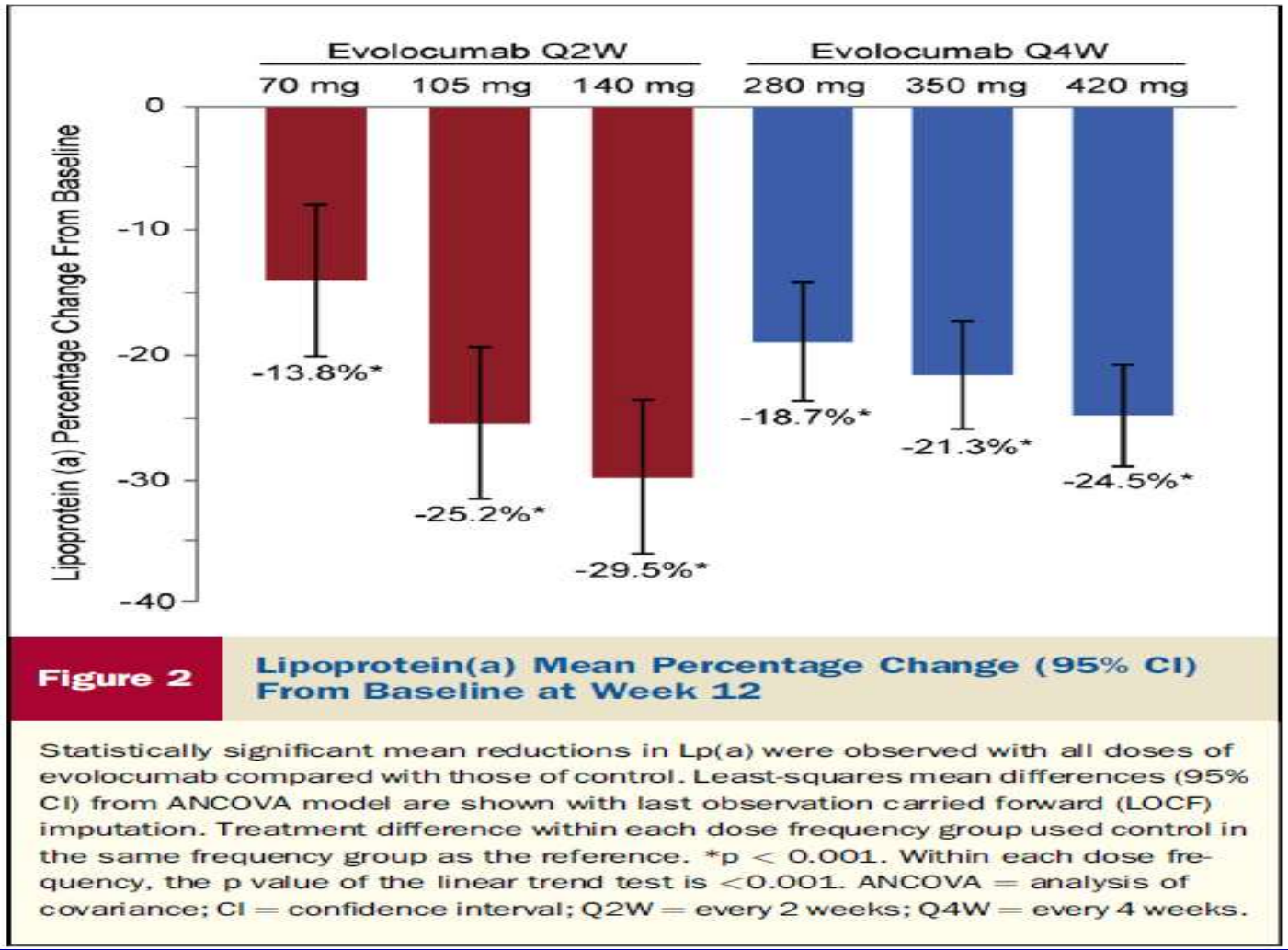



**Figure 2** **Lipoprotein(a) Mean Percentage Change (95% CI) From Baseline at Week 12**

Statistically significant mean reductions in Lp(a) were observed with all doses of evolocumab compared with those of control. Least-squares mean differences (95% CI) from ANCOVA model are shown with last observation carried forward (LOCF) imputation. Treatment difference within each dose frequency group used control in the same frequency group as the reference. *$p < 0.001$. Within each dose frequency, the p value of the linear trend test is $<0.001$. ANCOVA = analysis of covariance; CI = confidence interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Raal, F. J., et. al. (2014). Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): A Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials. *J Am Coll Cardiol, 63*(13), 1278-1288.

# Evolocumab Lowers Lipo (a)

- Reductions not associated with age or gender
- Reductions were greater in those on statins
- Reductions were greater when lipo (a) was >125 nmol/l.

Raal, F. J., et. al. (2014). Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): A Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials. *J Am Coll Cardiol, 63*(13), 1278-1288.

# Evolocumab Added to Statin Therapy

- LDL-C Assessment with PCSK9 MonoclonalL Antibody Inhibition Combined With Statin ThErapy – 2 (LAPLACE-2) Study.

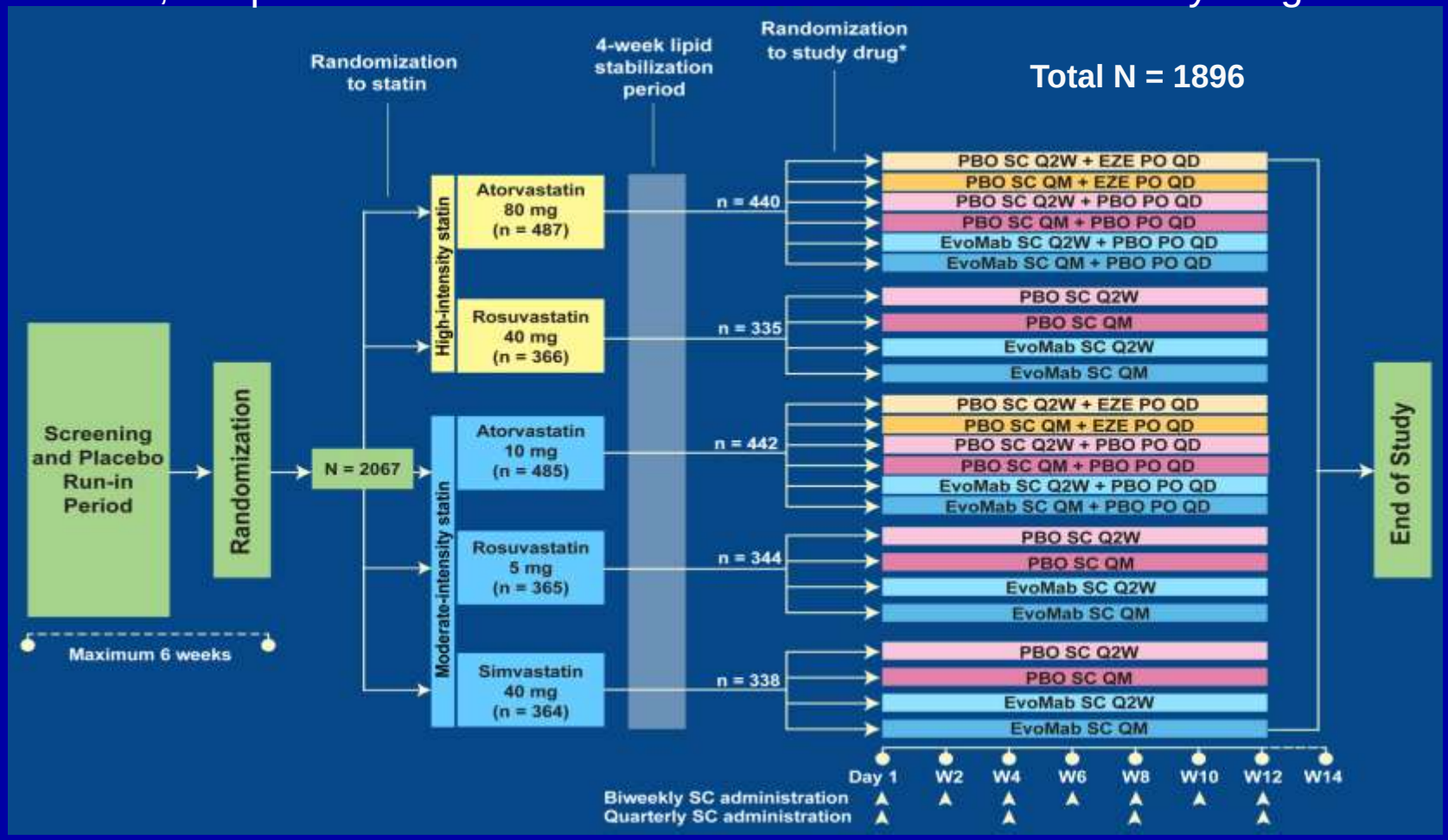
- Design:
  A 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, phase III study.

- Objective:
  To evaluate the efficacy and safety of evolocumab administered biweekly (140 mg) or monthly (420 mg) in combination with a statin in hypercholesterolemic patients.

Robinson, J. G., et. al. (2014). *JAMA, 311*(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Study Design

1,896 pts randomized to receive at least one dose of study drug.




Robinson, J. G., et. al. (2014). Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia. *JAMA, 311*(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Baseline Characteristics

| | Any Statin + Placebo (N = 558) | Atorvastatin + Ezetimibe (N = 221) | Any Statin + Evolocumab (N = 1117) |
|---|---|---|---|
| Age (years), mean (SD) | 60 (10) | 61 (9) | 60 (10) |
| Female, % | 48 | 49 | 44 |
| Coronary artery disease, % | 22 | 17 | 24 |
| Peripheral arterial disease or cerebrovascular disease, % | 10 | 9 | 11 |
| Diabetes mellitus, Type 2, % | 13 | 20 | 16 |

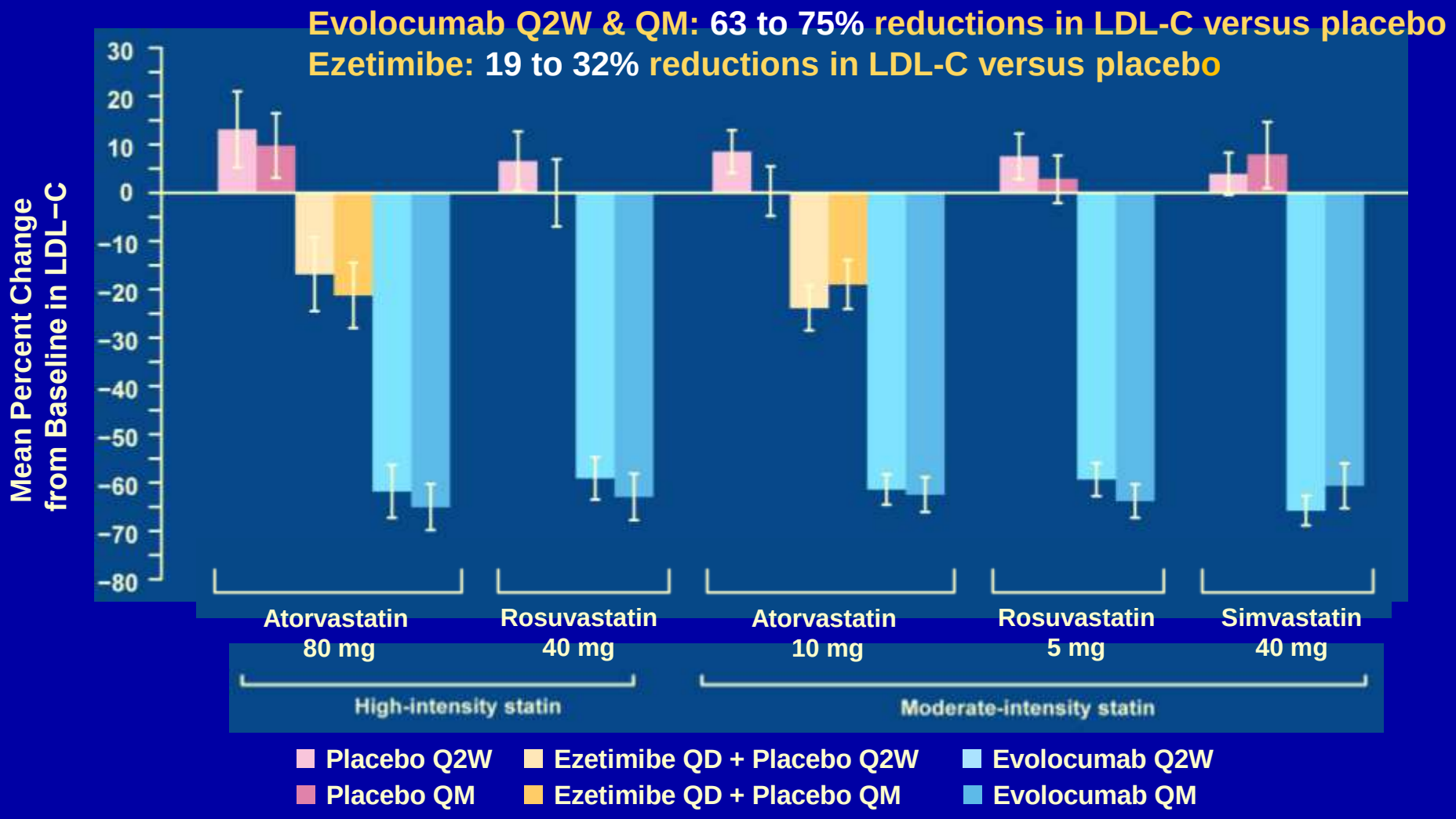
Robinson, J. G., et. al. (2014). Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia. JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Baseline Lipids

| | Any Statin + Placebo (N = 558) | Atorvastatin + Ezetimibe (N = 221) | Any Statin + Evolocumab (N = 1117) |
|---|---|---|---|
| | | | |
| LDL-C,[a] mg/dL, mean (SD) | 108 (40) | 109 (37) | 110 (42) |
| ApoB, g/L, mean (SD) | 88 (25) | 90 (25) | 90 (27) |
| TG, mg/dL, mean (SD) | 129 (66) | 136 (77) | 137 (82) |
| HDL-C, mg/dL, mean (SD) | 55 (17) | 52 (15) | 53 (16) |
| Lp(a), mg/dL, mean (SD) | 86 (100) | 92 (104) | 91 (113) |
| PCSK9, ng/mL, mean (SD) | 353 (114) | 351 (112) | 355 (111) |

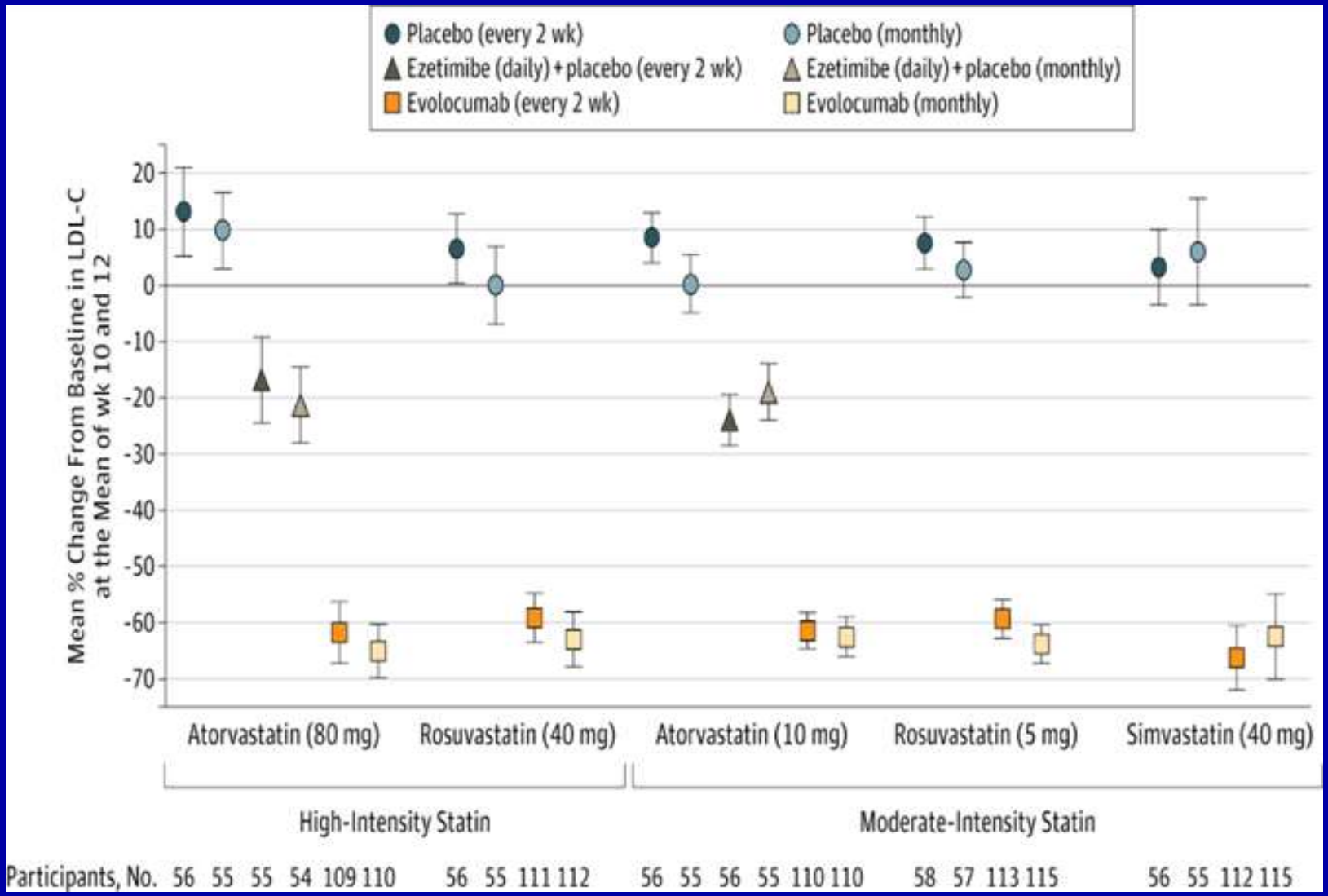
Robinson, J. G., et. al. (2014). Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia. JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: LDL-C Response at Mean of 12 Weeks



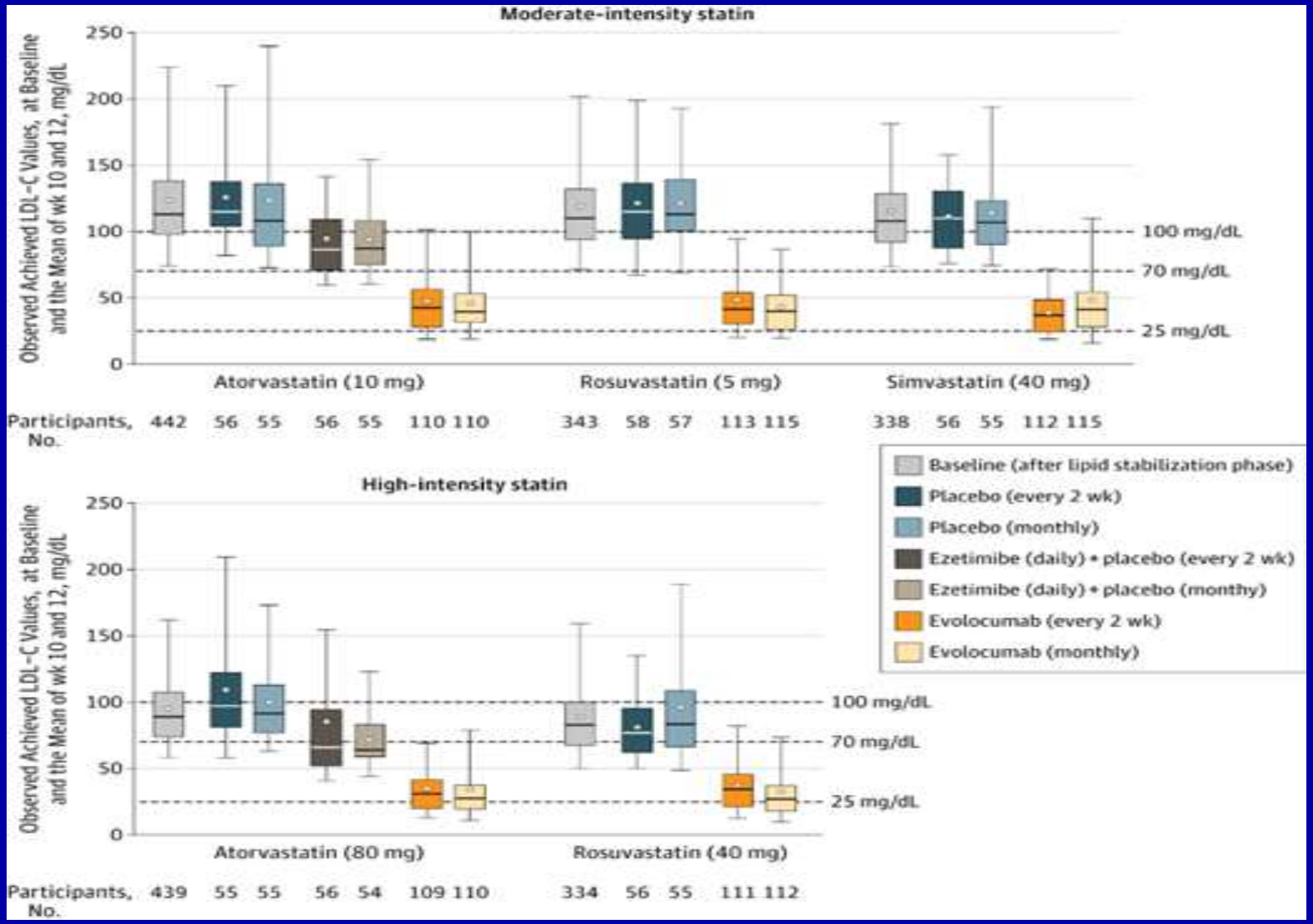

Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: LDL-C Response at Mean of 12 Weeks




Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

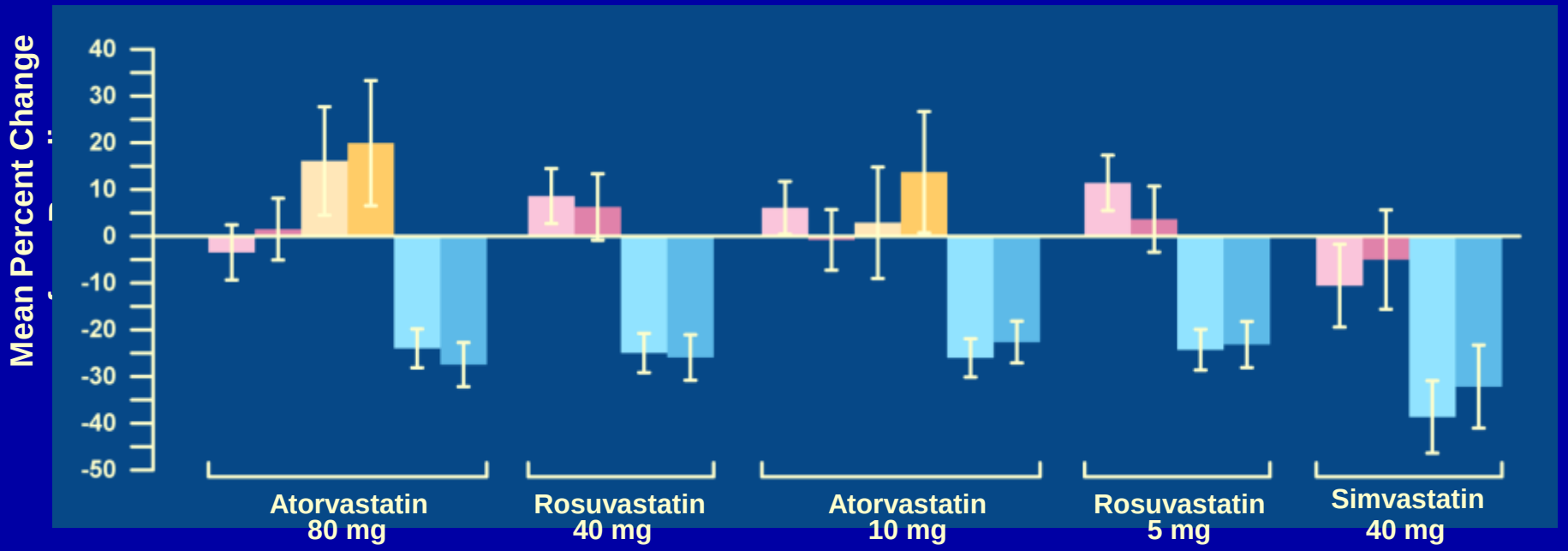
# LAPLACE-2: LDL-C Response at Mean of 12 Weeks




Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Lipo (a) Mean Weeks 10/12

**Lipoprotein (a)** Q2W **–21 to –36%** vs placebo




Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Safety and Tolerability

| n (%) | Any Statin + Placebo (N = 558) | Atorvastatin + Ezetimibe (N = 221) | Any Statin + Evolocumab (N = 1117) |
|---|---|---|---|
| Treatment-emergent AEs | 219 (39) | 89 (40) | 406 (36) |
| Most common AEs[a] | | | |
| Back pain | 14 (3) | 7 (3) | 20 (2) |
| Arthralgia | 9 (2) | 4 (2) | 19 (2) |
| Headache | 15 (3) | 5 (2) | 19 (2) |
| Muscle spasms | 6 (1) | 6 (3) | 17 (2) |
| Pain in extremity | 7 (1) | 3 (1) | 17 (2) |
| Serious AEs | 13 (2) | 2 (1) | 23 (2) |
| AEs leading to study drug discontinuation | 12 (2) | 4 (2) | 21 (2) |
| Deaths | 1 (0.2) | 0 (0)[b] | 0 (0) |
| CK > 5 x ULN | 2 (0.4) | 0 (0) | 1 (0.1) |
| ALT or AST > 3 x ULN | 6 (1) | 3 (1) | 4 (0.4) |
| Potential injection site reactions[c] | 8 (1) | 2 (1) | 15 (1) |
| Neurocognitive AEs | | | |
| Cognitive deterioration | 0 (0) | 1 (0.5) | 0 (0) |
| Disorientation | 0 (0) | 1 (0.5) | 0 (0) |
| Post-baseline binding antibodies | NA | NA | 1 (0.1)[d] |

Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# LAPLACE-2: Conclusions

- Evolocumab significantly lowered LDL-C at the mean of weeks 10/12 in patients with hypercholesterolemia on background statin therapy.
  - There were no notable differences in percent reductions for moderate and high-intensity background statin therapies.
- Evolocumab 140 mg biweekly and 420 mg monthly dosing regimens are clinically equivalent.
- When combined with atorvastatin, LDL-C lowering was significantly greater in patients receiving evolocumab (63-75%) versus those receiving ezetimibe (19-32%).
- LDL-C < 70 mg/dL was achieved in most patients on evolocumab.
  - 86-94% (moderate-intensity statin)
  - 93-95% (high-intensity statin)
- There were no notable differences in safety & tolerability in evolocumab-, placebo-, and ezetimibe-treated patients.

Robinson, J. G., et. al. (2014). JAMA, 311(18), 1870. doi: 10.1001/jama.2014.4030

# BDM Thoughts

- This product is a gorilla for lipids including lipo (a) ☺
- We need inflammatory results along with CV outcome results
- Could improve compliance with once a month subq injection!!

# FOURIER

- An ASCVD outcomes trial is underway
  - Evolocumab Q2W or QM added to moderate or high intensity statin therapy
  - Patients are those with clinical ASCVD (N = 22,500)
  - The trial is evaluating atherosclerotic cardiovascular disease (ASCVD) event reduction and safety

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER). Available at: http://clinicaltrials.gov/ct2/show/NCT01764633.

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

- Retrospective analysis 576 pts; rx'ed in prevention clinic 2000 -2008; mean age 55.5 yo; 39% female.

- Latent growth-curve analysis was used in modeling changes in outcome measures.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

**TABLE 2 Baseline Patient Demographic Characteristics (N = 576)**

| Characteristic | n (%) or Mean ± SD |
|---|---|
| Age, y | 55.5 ± 10.2 |
| BMI, kg/m$^2$ | 27.5 ± 5.0 |
| Male | 344 (61) |
| White | 576 (100) |
| Current or past smoker | 209 (36) |
| Diabetes | 25 (5) |
| Hyperlipidemia | 512 (89) |
| Hypertension | 325 (58) |
| CAD/CAD equivalent | 143 (25) |
| Metabolic syndrome | 321 (56) |
| Insulin resistant | 417 (73) |
| Adjusted Framingham Risk Score | |
| <10% | 370 (66) |
| 10%–20% | 141 (24) |
| >20% | 58 (10) |
| Carotid plaque—PBS score ≥1.2 mm | (85) |

Abbreviations: BMI, body mass index; CAD, coronary artery disease; PBS, plaque burden score.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

**TABLE 1 Components of the Bale/Doneen Method**

| Components | Description |
|---|---|
| 1. Education | Each patient is educated about the disease state of atherosclerosis and understands how myocardial infarctions and ischemic strokes occur. |
| 2. Disease | Each patient is evaluated for the presence of atherosclerosis, using noninvasive office-based techniques, to find asymptomatic vascular disease, and is monitored annually with an intima-media thickness (IMT) test to follow the individual trajectory of atherosclerotic disease. In addition, all patients are monitored annually with a carotid IMT test to follow the atherosclerotic disease over time in the individual patient. |
| 3. Inflammation | Biomarkers are used to routinely determine the inflammatory state of the vascular system. Endothelial markers include hs-C-reactive protein, microalbumen/creatinine urine ratio, and fibrinogen. Lipoprotein-associated phospholipase $A_2$ is evaluated for intima activity. Patients were instructed to have these assessed at least biannually. |
| 4. Root causes | The root cause or causes of the atherosclerotic process are determined and managed for each patient. Root causes of atherosclerosis can include insulin resistance, lipo(a), familial hyperlipidemia, potentially myeloperoxidase, and vitamin D deficiency.[51] Appropriate follow-up testing for effective management of a root cause was done on average quarterly to semiannually. |
| 5. Optimal goals | Goals of therapy are set based on peer-reviewed, reliable research and guidelines, with optimal targets in an attempt to minimize risk and often going beyond the values set for the standard of care. Attainment of goals was evaluated, on average, every 3–6 months. |
| 6. Genetics | Genetic information is obtained on patients to aid in the assessment of their cardiovascular risk and to help guide therapy. These tests were never repeated. Their clinical utility never expires, unlike other biomarkers. This makes them arguably the least expensive tests performed. |

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

- Mean cIMT score decreased by 0.01mm/yr – $p<0.001$
- cIMT plaque burden score decreased by 0.17mm/yr- $p<0.001$

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

Findings suggest that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

The Bale/Doneen Method was developed for the prevention and treatment of heart attacks and ischemic strokes in all primary and secondary prevention patients.

This method is now being integrated nationally into primary care clinics and specialty clinics around the country.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

The Bale/Doneen Method is a method of delivering evidence- and outcome-based medical care using a system anchored in the disease of atherosclerosis rather than the standard practice of delivering preventative care based solely on risk factors.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

## What's New and Important

- The Bale/Doneen Method rests on a platform of assessing and monitoring arterial disease. It is anchored in inflammation being causal of atherosclerosis. The method comprehensively evaluates known sources for arterial inflammation and promotes optimal management of all identified contributors to the arterial ''fire.'' The methods of assessing and treating patients used by the Bale/Doneen Methods are available to any practitioner.
- Previous studies have indicated that patients who receive prevention and treatment of CVD through the Bale/Doneen Method show stabilization of the atherosclerotic disease process, a significant conversion of plaque morphology to 100% echogenic lesions by the fifth year of follow-up, and that echogenic carotid plaque is significantly less inflamed than nonecogenic plaque. Consistent with past studies, this article shows that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.
- The use of growth-curve modeling in examining changes in markers such as IMT and other biomarkers associated with CVD can improve the accuracy of CVD

Feng, D., et. al. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

# Arterial Wellness Can Be Achieved

- We live in an era of technology sufficient to identify subclinical arterial disease and knowledge necessary to halt atherosclerosis.

- Inflammation is causal of atherosclerosis.

- Numerous health issues can produce arterial inflammation.

Bale BF, Doneen AL (2014) A Guarantee of Arterial Wellness: New Era of Cardiovascular Medicine. J Clin Exp Cardiolog 5:298. doi: 10.4172/2155-9880.1000298Reference

# Arterial Wellness Can Be Achieved

- Individuals can be assessed for which particular inflammatory issues are drving their disease.
- These conditions can be managed effectively enough to extinguish the inflammation.
- Underlying atherosclerosis will stabilize and remain quiescent.

Bale BF, Doneen AL (2014) A Guarantee of Arterial Wellness: New Era of Cardiovascular Medicine. J Clin Exp Cardiolog 5:298. doi: 10.4172/2155-9880.1000298Reference

# Upcoming Presentations

# Upcoming Presentations

- 5/15/14 – Brad speaking at dental meeting- Courtyard Marriott, 136 Marsh Hill Rd., Orange, CT
- 5/22/2014- book signing at Barnes & Noble, Cool Springs, TN at 7:00 PM
- 6/7/14 – Brad speaking at DO 2014 Joint Annual Convention- San Antonio, TX

# Open for Discussion