Bale/Doneen Live Chat Session

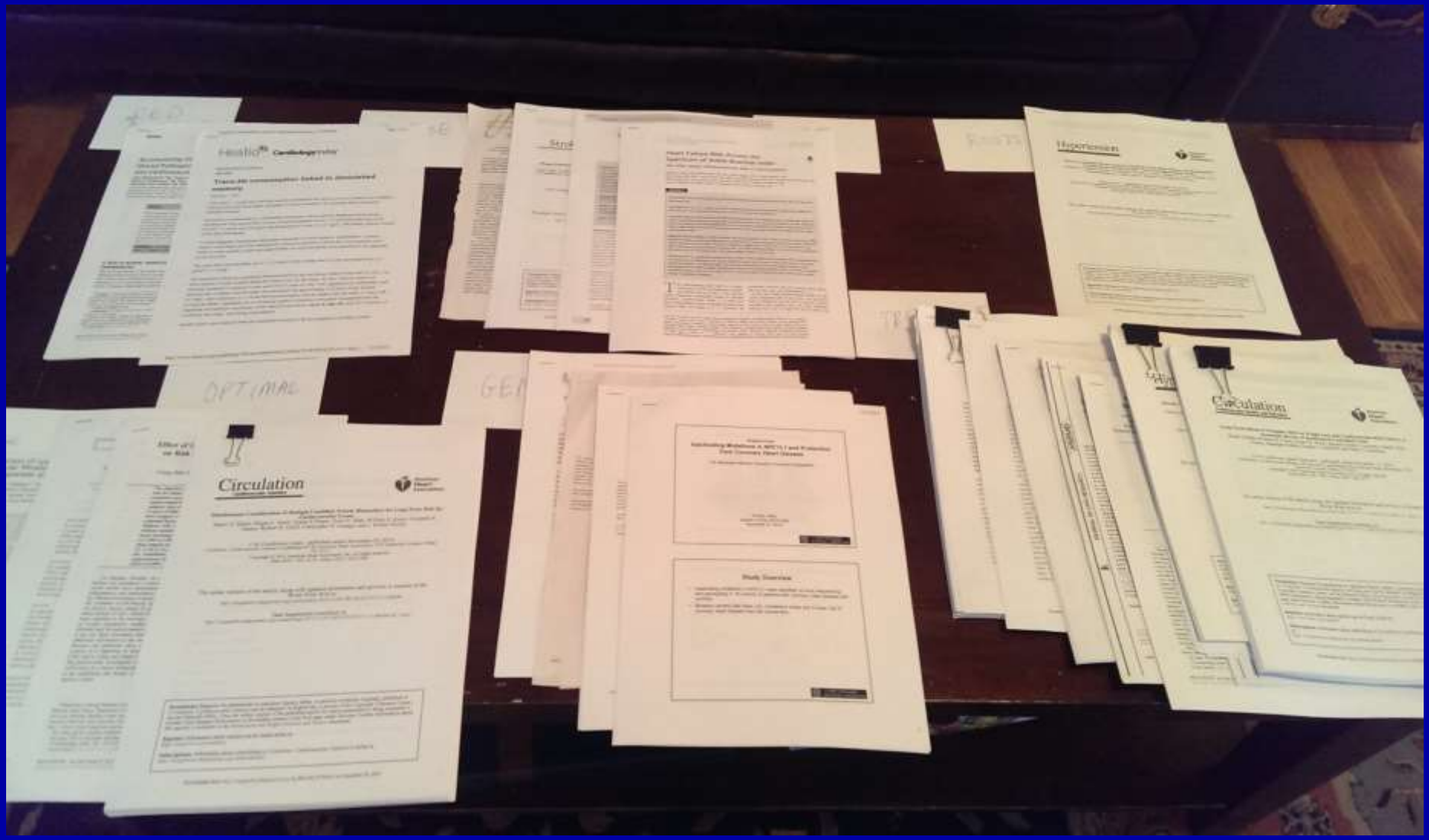
Amy Doneen DNP, ARNP

December 10, 2014

5:30-6:30 pm PST

Happy December from Spokane!

Today's chat: Post AHA….



Outline for today's discussion

1. Trans-fat and memory
2. Psoriasis and CVD
3. ABI and Heart Failure
4. Non-Calcified plaque and stroke risk
5. PerioProtect Method and Lp-PLA2
6. Diastolic Blood Pressure and Optimal Care
7. Low total Bilirubin levels
8. NT-proBNP and women
9. NPC1L1
10. Diets and long term value
11. Dietary Nitrates (beetroot juice) and BP
12. IMPROVE-IT
13. SEAS – Cancer risk
14. Dual Antiplatelet

Red Flags

Trans-fat and Memory loss

Trans-fat consumption causes memory loss

1,018 healthy participants with no previous diagnosis of heart disease, including 694 men aged at least 20 years old

LDL levels were between 115-190mg/dL

FBS <142 mg/dL

Mean daily trans-fat intake was 4.1 ± 2.9 g/day and ranged from 0.33 g/ay to 15.5g/day

Bui, A. Abstract #15572. Presented at: American Heart Association Scientific Sessions; Nov 15-19, 2014, Chicago

Trans-fat consumption causes memory loss

Results:

Trans-fat intake was adversely predictive of memory in men aged 30-45 year (n=146)

After adjustment for confounders, each gram/day of dietary trans-fat intake was associated with approximately 0.76 fewer words recalled (p=0.006), with a difference of 11 words between participants with the highest trans-fat intake vs those with no trans-fat intake.

Bui, A. Abstract #15572. Presented at: American Heart Association Scientific Sessions; Nov 15-19, 2014, Chicago

Trans-fat consumption causes memory loss

Bale/Doneen Take-Away:

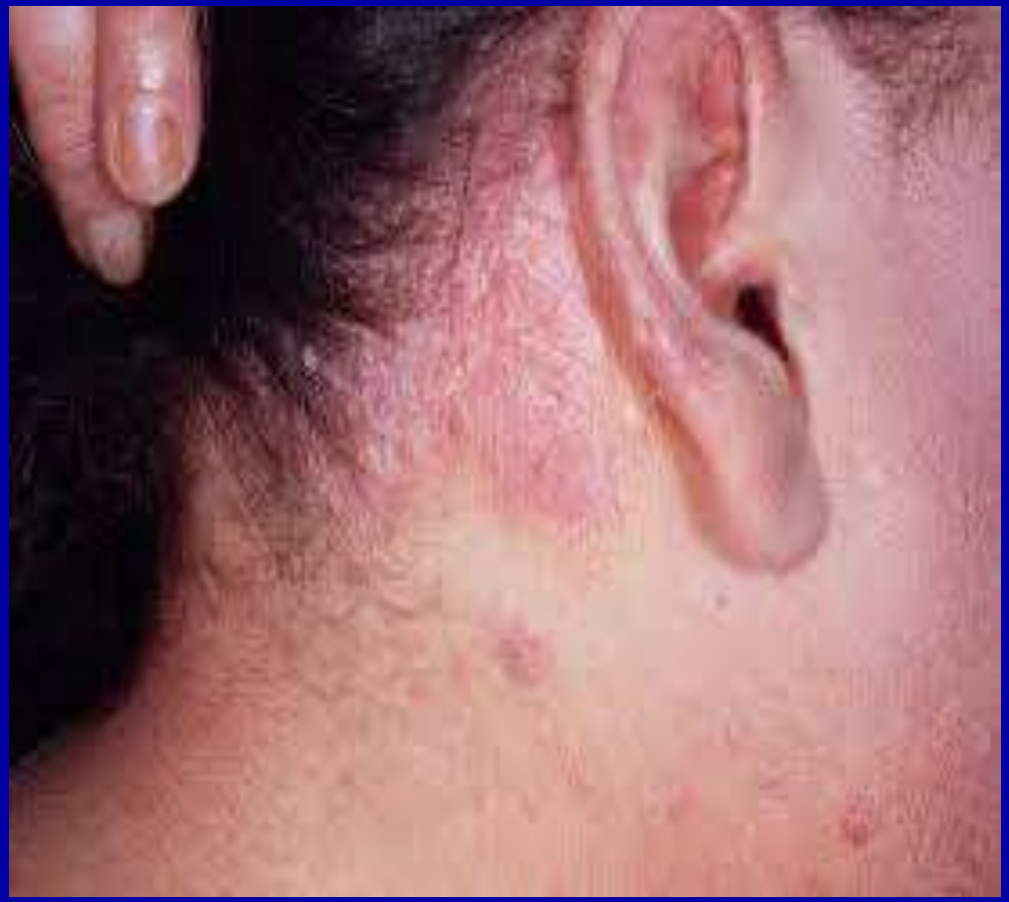
Nutrition Facts

Serving Size 2 tbsp (32g) unpopped (makes 4 cups popped)
Servings Per Bag about 3
Servings Per Box about 28

Amount Per Serving	2 Tbsp Unpopped	1 cup Popped
Calories	170	30
Calories from Fat	100	20
	% Daily Value**	
Total Fat 12g*	18%	3%
Saturated Fat 2.5g	13%	0%
Trans Fat 4.5g		
Polyunsaturated Fat 0.5g		
Monounsaturated Fat 2.5g		
Cholesterol 0mg	0%	0%
Sodium 380mg	16%	3%
Potassium 0mg	0%	0%
Total Carbohydrate 14g	5%	1%
Dietary Fiber 3g	12%	0%
Protein 2g		

Bui, A. Abstract #15572. Presented at: American Heart Association Scientific Sessions; Nov 15-19, 2014, Chicago

Psoriasis and CVD



Psoriasis and CV-related Co-morbidities

November 2013 – International Psoriasis Council: Global focus group assembled – dermatology, immunology, and cardiology.

Goal of the group: better understand the inflammatory role of psoriasis in the induction of cardiometabolic disease.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Psoriasis and CV-related Co-morbidities

Diabetes:

Mild psoriasis had an OR of 1.53 for diabetes (95% CI), 1.16-2.04)

Moderate to severe psoriasis OR of 1.97 for diabetes (95% CI), 1.48-2.62)

Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. *JAMA Dermatol*. 2013;149:84-91.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Psoriasis and CV-related Co-morbidities

Chronic Kidney Disease (CKD):

Psoriasis had an OR of 1.13 for CKD
(95% CI, 1.11-1.15)
*adjusted for age, gender, diabetes, HTN, cyclosporine, psoriatic arthritis, and use of NSAIDs

Mild to moderate Psoriasis and CKD – 1.08 and 1.90

Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ*. 2013;347:f5961.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Psoriasis and CV-related Co-morbidities

Cardiovascular Disease:

Severe psoriasis associated with a 50% increased risk of mortality and as many as 5 years lost life explained by cardiovascular disease, infection, and cancer.

Interaction between severe psoriasis and the first cardiovascular event at 40 years old.

Younger patients with severe psoriasis have a 2.5-fold higher risk of dying of cardiovascular event compared with controls.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1735-1741.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Psoriasis and CV-related Co-morbidities

Currently recruiting for: the Vascular Inflammation in Psoriasis trial (VIP) –

Recruiting 96 patients with moderate-to-severe psoriasis for an interventional study randomized to intensive treatment with adalimumab, phototherapy or placebo –

Aim: to understand effects on vascular inflammation and cardiometabolic disease biomarkers, FDG PET/CT.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Psoriasis and CV-related Co-morbidities

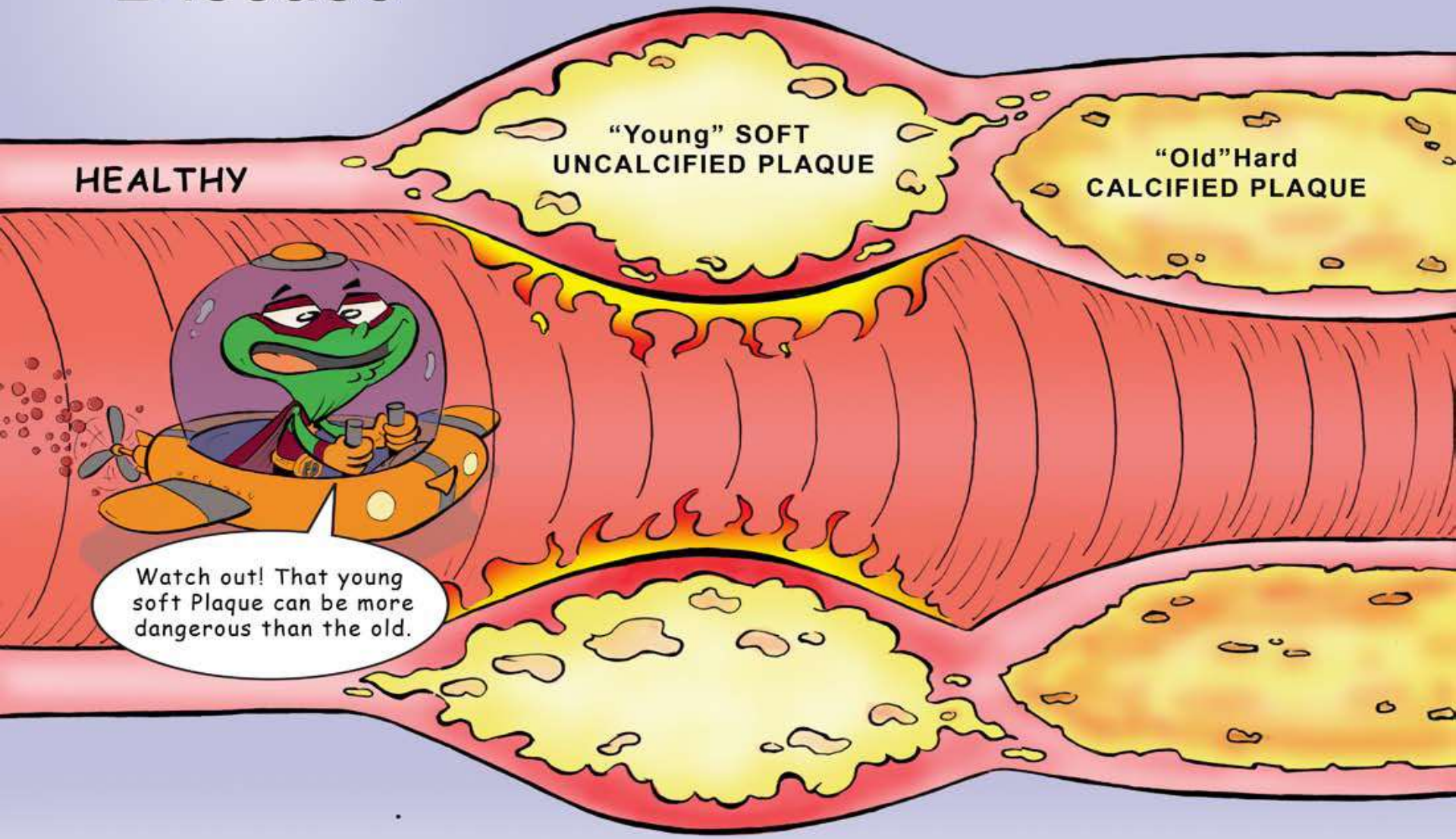
Bale/Doneen Take-Away and Clinical Significance:

Shared pathways between psoriasis skin inflammation and atherosclerosis – including pathways involving neutrophils and T-cells.

Application of imaging strategies has proven psoriasis to be a systemic inflammatory disease with increased inflammation detected in skin, joints, and blood vessels.

Shlyankevich, J., Nehal, M., Krueger, J., et al. Accumulating evidence for the Association and shared pathogenic mechanisms between psoriasis and cardiovascular-related Comorbidities. The American Journal of Medicine. (Dec 2014) 127, 1148-1153.

Disease



Plaque formation is an active process and its consistency changes over time. Some technologies (X-Rays) can only see hard calcified disease while others like ultrasounds can spot soft disease.

Dale Doneen METHOD

Moss Freedman

ABI and heart failure

ABI <1.0 associated with risk of heart failure

Atherosclerosis Risk in Communities) Study – ARIC – 1987-1989

ABI measurements available in 13,150 patients free from previous HF. Followed mean 17.7 years. 1,809 incidence HF events occurred.

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. Dec 2014.

ABI <1.0 associated with risk of heart failure

ABI < 1.0 compared to ABI 1.01-1.40, associated with a 40% increased risk of incident HF events.

(HR 1.40; 95% CI:1.12-1.74)

Adjusted for traditional HF risk factors, prevalent coronary heart disease, subclinical carotid atherosclerosis, and interim myocardial infarction.

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

ABI <1.0 associated with risk of heart failure

ARIC protocol for ABI measurements – automated oscillometric device – calculated as the ratio of lower extremity (one randomly selected leg) to upper extremity (R. brachial pressure)

ABI categories <0.90, 0.91 to 1.00, 1.01 to ≤1.40, and > 1.40.

Incident Heart Failure (HF) defined as first hospitalization with internaltion classification of diseases

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

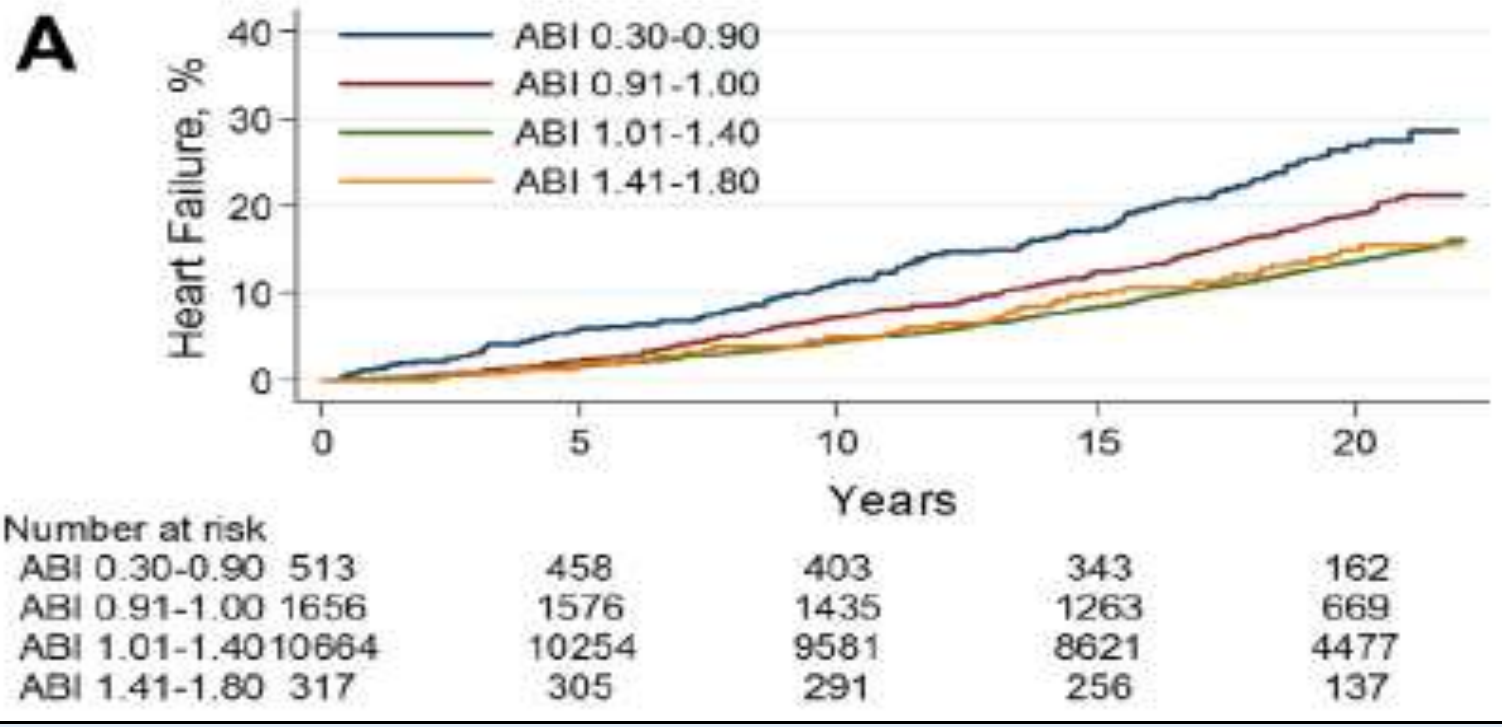
ABI <1.0 associated with risk of heart failure

TABLE 1 Baseline Characteristics of 13,150 ARIC Participants Free From Prevalent HF According to Category of ABI

Variable	ABI ≤0.90 (n = 513 [3.9%])	ABI 0.91-1.00 (n = 1,656 [12.6%])	ABI 1.01-1.40 (n = 10,664 [81.1%])	ABI >1.40 (n = 317 [2.4%])	p Value for Trend
ABI	0.84 (0.79-0.88)	0.97 (0.94-0.99)	1.16 (1.09-1.23)	1.44 (1.42-1.49)	
Age (yrs)	56 (50-61)	54 (49-59)	54 (49-59)	56 (50-60)	0.18
Women	354 (69.0%)	1,170 (70.7%)	5,547 (52.0%)	132 (41.6%)	<0.001
African American	156 (30.4%)	428 (25.9%)	2,714 (25.5%)	54 (17.0%)	0.005
CHD	30 (5.8%)	75 (4.5%)	393 (3.7%)	21 (6.6%)	0.15
Carotid plaque*	194 (48.5%)	488 (38.8%)	2,767 (33.4%)	79 (34%)	<0.001
Hypertension	228 (44.4%)	581 (35.1%)	3,317 (31.1%)	93 (29.3%)	<0.001
Diabetes mellitus	74 (14.4%)	187 (11.3%)	1,079 (10.2%)	38 (10.0%)	0.025
Obesity†	142 (27.7%)	493 (29.8%)	2,688 (25.2%)	88 (27.8%)	0.001
CKD	31 (6.0%)	52 (3.1%)	251 (2.4%)	12 (3.8%)	<0.001

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

ABI <1.0 associated with risk of heart failure



Number at risk

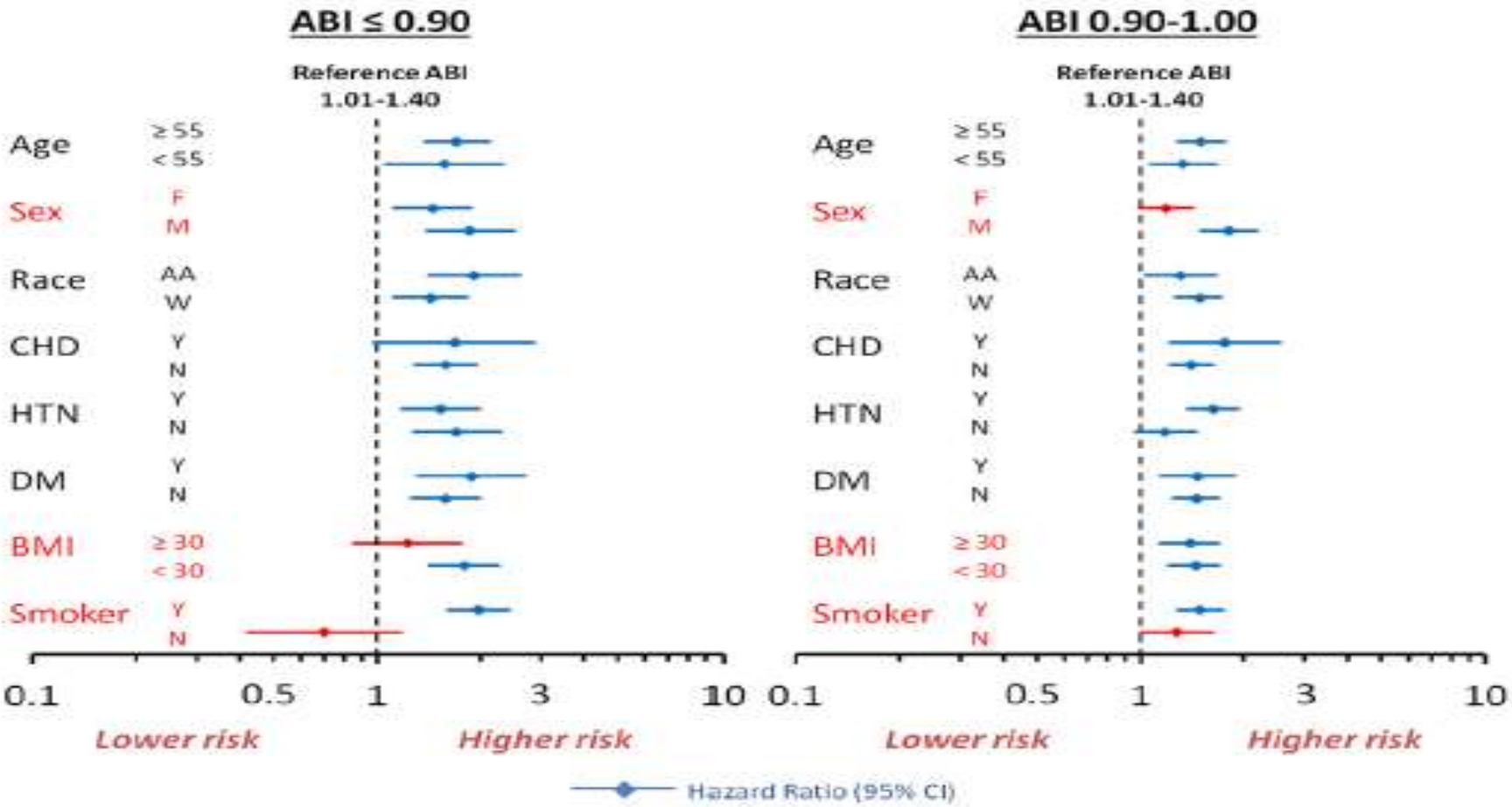
ABI 0.30-0.90	513	458	403	343	162
ABI 0.91-1.00	1656	1576	1435	1263	669
ABI 1.01-1.40	10664	10254	9581	8621	4477
ABI 1.41-1.80	317	305	291	256	137

FIGURE 1 **Incident HF According to Categories of ABI in the ARIC Study**

(A) Cumulative incidence plot for heart failure (HF) according to ankle-brachial index (ABI).

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

ABI <1.0 associated with risk of heart failure



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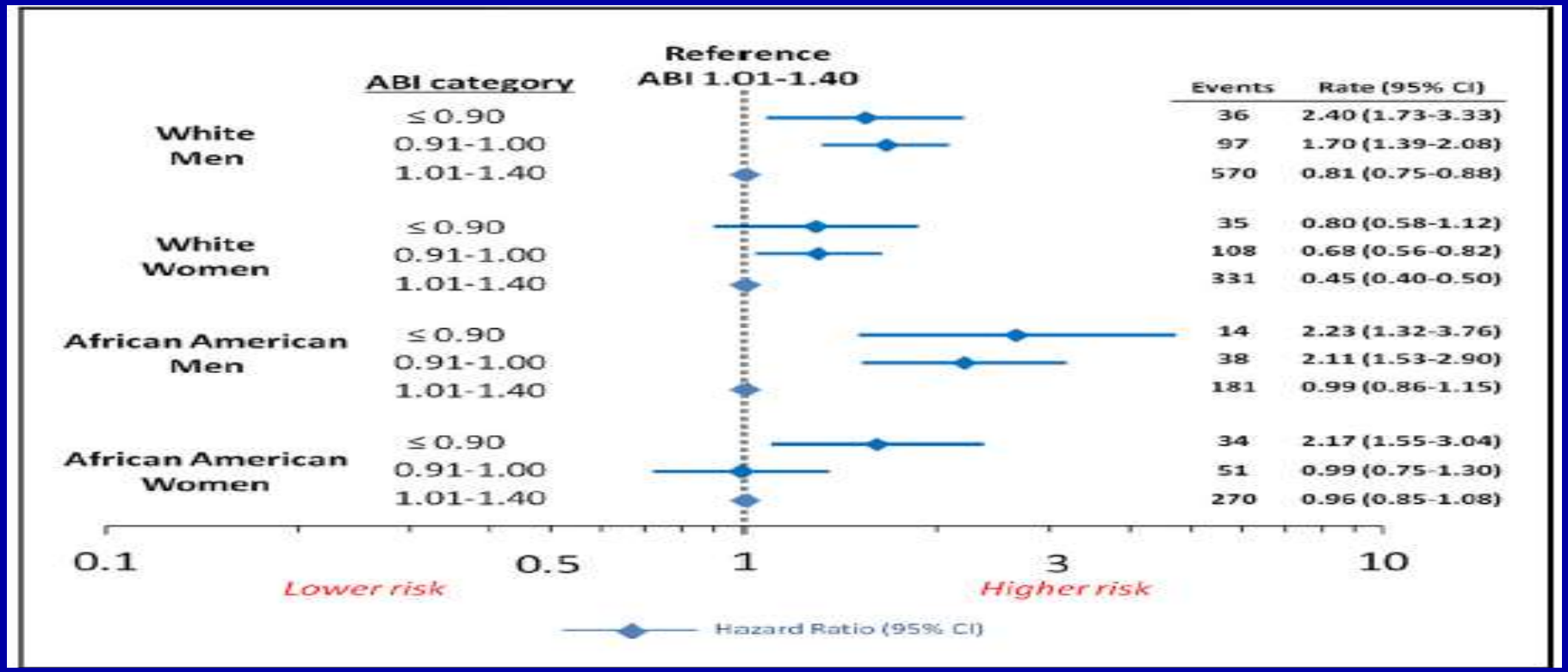
ABI <1.0 associated with risk of heart failure



ABI <.90 – 40% increased risk **HR: 1.40 (95% CI, 1.12-1.74)**

ABI 0.91-1.00 – 36% increased risk **HR: 1.36 (95% CI, 1.17-1.59)**

Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

ABI <1.0 associated with risk of heart failure

Bale/Doneen Take-Away:

1 in 6 of participants in the ARIC trial had low ABI which is comparable to other population based populations (13-18%).

ABI is a simple, noninvasive measure known to be associated with atherosclerotic vascular disease and now has associated increased risk for heart failure when < 1.00.

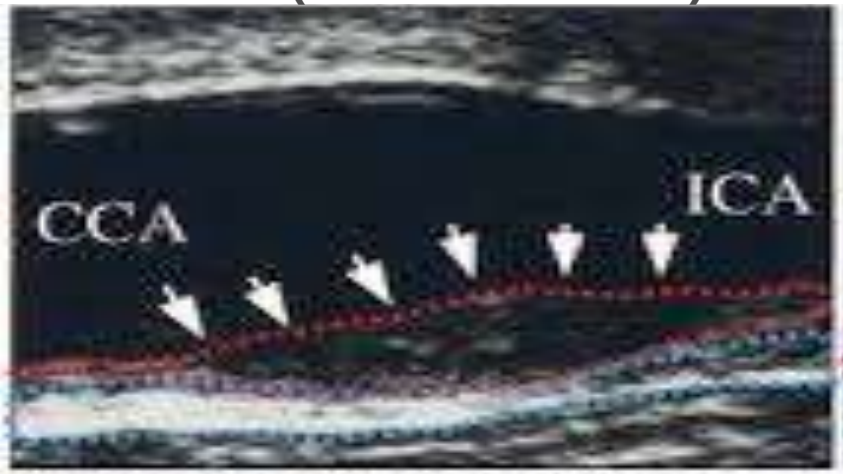
Our recommendation to do ABI at age 50 years old with one or more risk factor fits well into this data.

Don't judge on who to do ABI based on gender, DM, BP, BMI

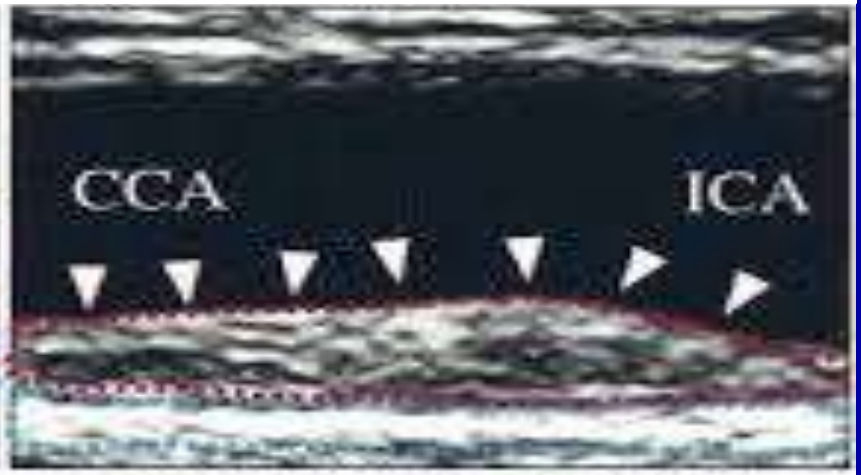
Gupta, Deepak, Skali, H, Claggett, B. Heart Failure Risk across the spectrum of ABI. JACC. Vol 2 NO 5. 447-54. Dec 2014.

Non-calcified (echolucent) plaque and Stroke Risk

Echolucent (unstable/soft/het)



Echogenic (stable/calcified)



Plaque echolucency and stroke risk in asymptomatic stenosis

Systematic review and meta-analysis to summarize the association between ultrasound-determined carotid plaque echolucency and future ipsilateral stroke risk.

Conflicting data in the literature regarding the predictive value of carotid plaque echolucency.

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

Systematic review and Meta-analysis – Screened total of 5409 abstracts from which 8 manuscripts were deemed to meet inclusion criteria.

Definition: Echolucent: lipid-rich plaque (noncalcified).

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

Studies 7557 subjects with a mean follow-up of 37.2 months, yielding a total of 23,410.2 person years of follow-up

Found a significant positive relationship between plaque echolucency and the risk of future ipsilateral stroke; RR of 2.31 (95% CI. 1.58-3.39, $p<0.001$)

Of the total study sample, 1741 subjects (23%) had a positive carotid ultrasound or echolucency, whereas 5816 (77%) has a negative test for echolucency.

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

In the echolucent-positive (non-calcified) test group, 141 ipsilateral strokes occurred compared with 100 ipsilateral strokes with the echolucent negative group.

The cumulative incidence of ipsilateral stroke in the echolucent plaque cohort was 5.7% compared with 2.4% in the non-echolucent plaque cohort.

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

The degree of carotid stenosis criteria alone within the 50%-99% range provides a relatively weak means for clinically stratifying the risk for ipsilateral stroke in asymptomatic persons.

In patients with 50%-99% carotid stenosis, found a 2.6-fold increase risk of ipsilateral stroke if the plaques were predominately echolucent (soft) compared with plaques, which were stable (calcified).

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

Meta-analysis calculated – future stroke

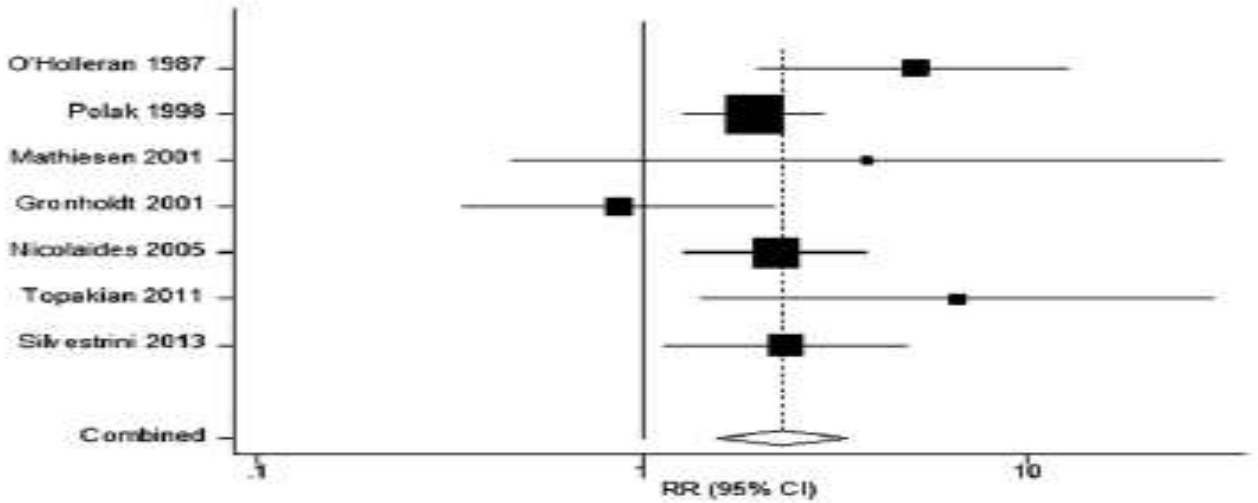


Figure 1. Forest plot of the association between ultrasound-determined plaque echolucency and future ipsilateral stroke. Meta-analysis calculated using a random-effects model. Squares represent point estimates for the effect size expressed as a relative risk (RR). The size of the squares is proportional to the inverse of the variance of the estimate. Diamond represents the pooled estimate and the horizontal lines represent the 95% confidence intervals (CI).

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

Meta – analysis in patients with ≥ 50% stenosis

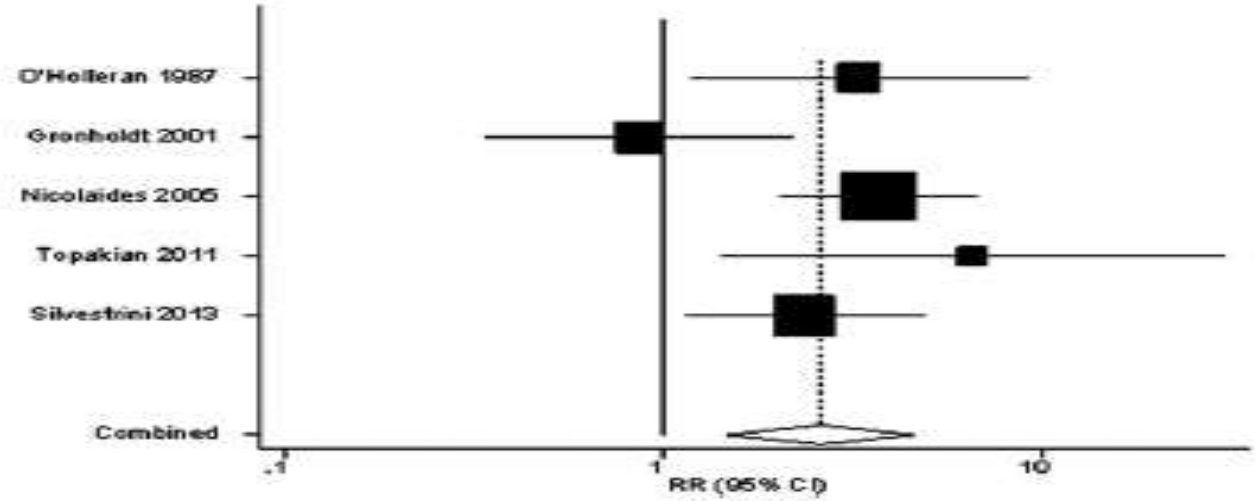


Figure 2. Forest plot of the association between ultrasound-determined plaque echolucency and future ipsilateral stroke in the subgroup of patients with ≥50% stenosis. Meta-analysis calculated using a random-effects model. Squares represent point estimates for the effect size expressed as a relative risk (RR). The size of the squares is proportional to the inverse of the variance of the estimate. Diamond represents the pooled estimate and the horizontal lines represent the 95% confidence intervals (CI).

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.

Plaque echolucency and stroke risk in asymptomatic stenosis

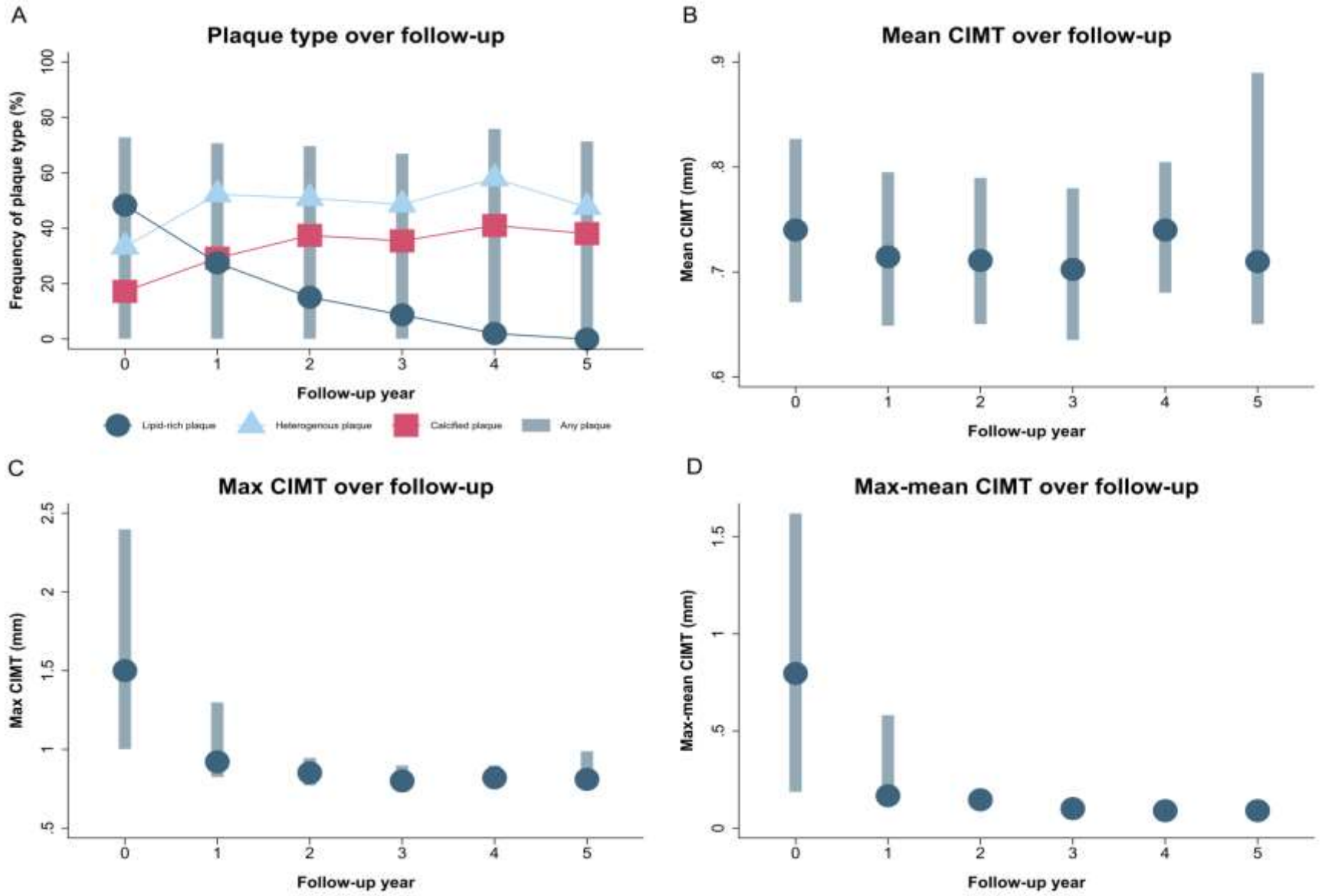
Bale/Doneen Take-Away:

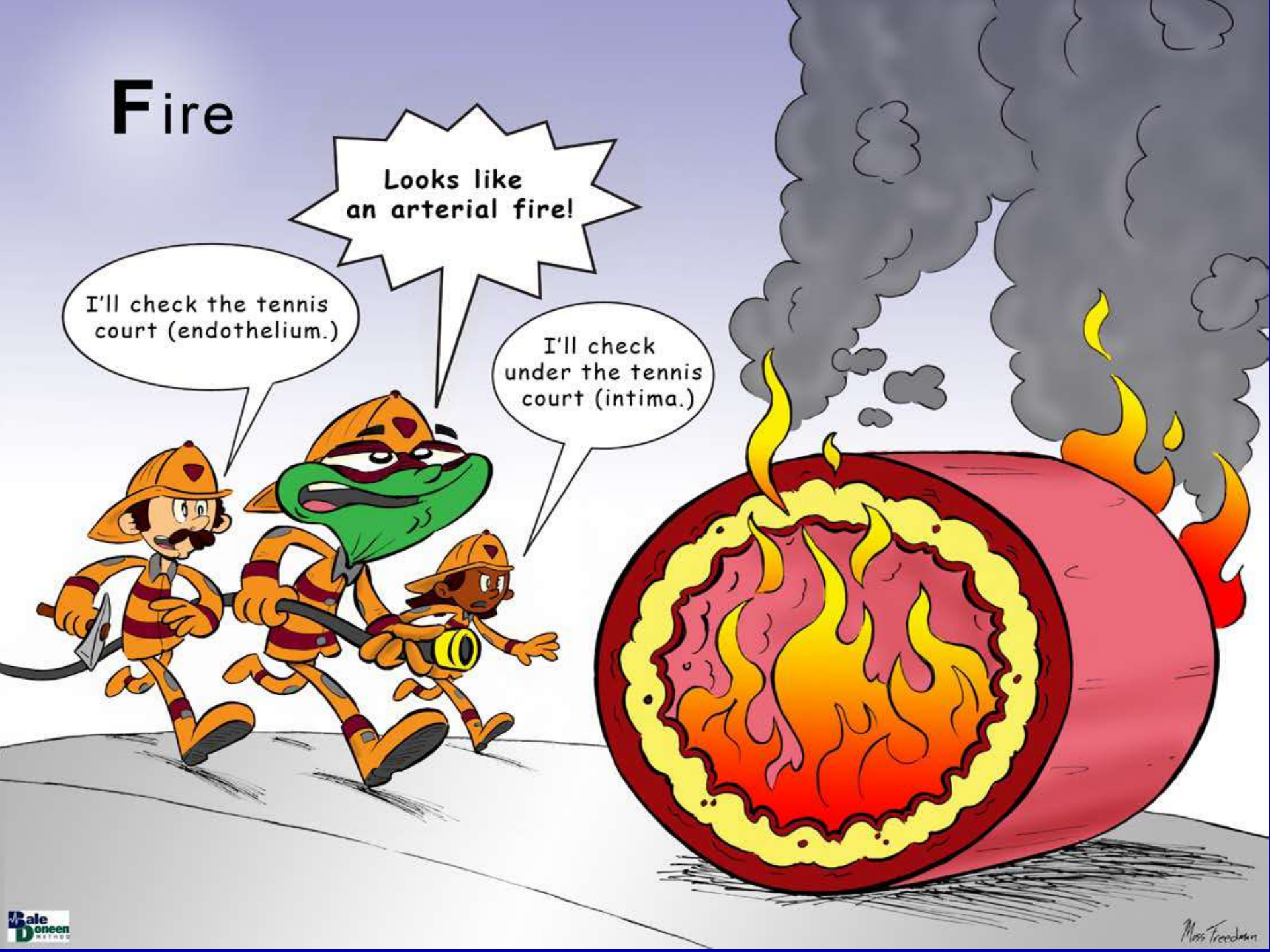
Although there was a lack of control with the protocols utilized for carotid IMT measurement techniques, the presence of echolucent (non-calcified) plaque is a risk factor for stroke regardless of stenosis.

Always couple structure with inflammatory bio-markers.

Assessing the “quality” of plaque is augmentative to stenosis.

Gupta, A., Kesavabhotla, K, Baradaran, H. Plaque Echolucency and Stroke Risk in Asymptomatic Carotid Stenosis. Stroke. 2015:46:00-00.




Fire
Looks like an arterial fire!
I'll check the tennis court (endothelium.)
I'll check under the tennis court (intima.)
Bale Doneen METHOD
Moss Freedman

PerioProtect Method lowers Lp-PLA2

Pilot Study with 6 subjects completed the 3 months trial.

Lp-PLA2 measured at baseline, 1 mo, 3 months.

1.7% hydrogen peroxide gel (PerioGel) and 1-3 drops/tray Vibramycin Syrum (50mg/5mg doxycycline).

Protocol:	>6mm pockets	4x/day x 15min
	3-6mm pockets	3 x day x 15min
	<3mm pockets	(maintenance)
		2 x day x 15 min

Keller, D. Systemic LpPLA2 cardiovascular marker response to direct medication delivery periodontal treatment. Cardiovascular System. December 2014. ISSN, 2052-4358.

PerioProtect Method lowers Lp-PLA2

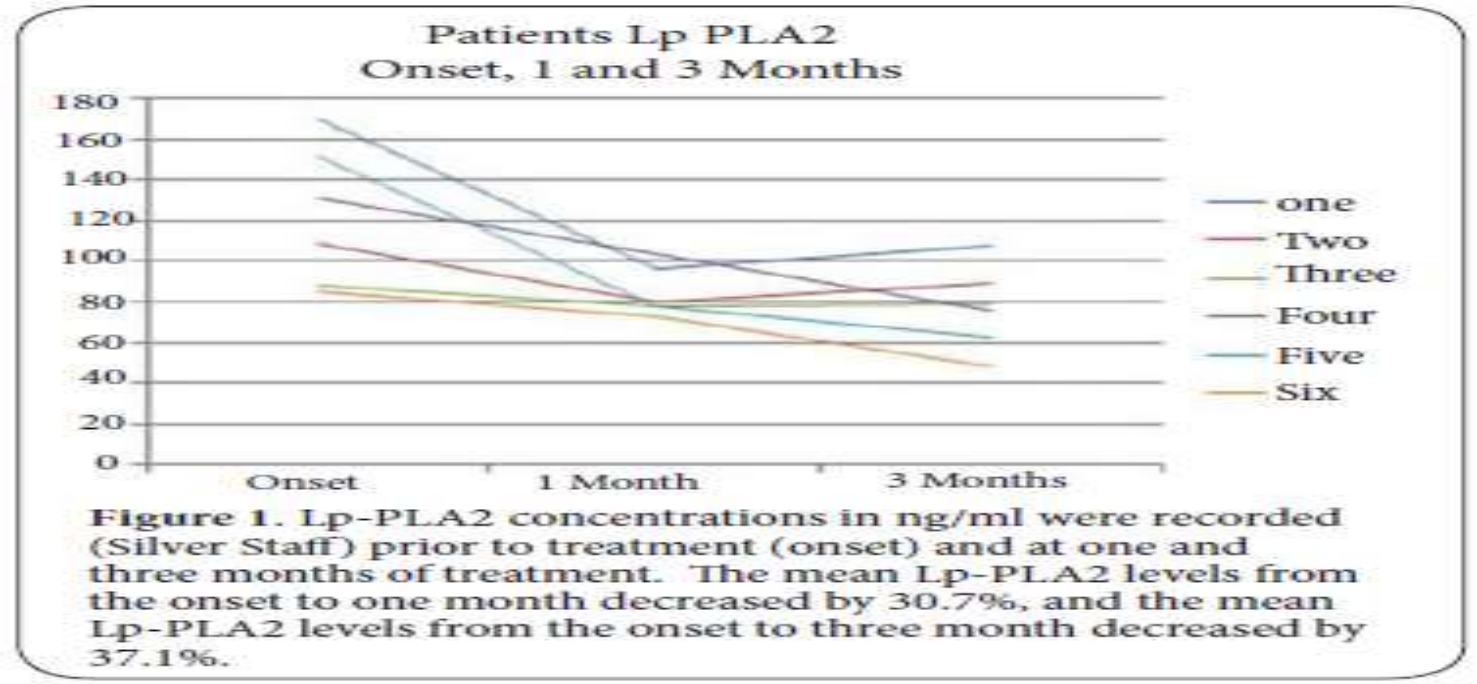


Figure 1. Lp-PLA2 concentrations in ng/ml were recorded (Silver Staff) prior to treatment (onset) and at one and three months of treatment. The mean Lp-PLA2 levels from the onset to one month decreased by 30.7%, and the mean Lp-PLA2 levels from the onset to three month decreased by 37.1%.

Lp-PLA2 (ng/mL) mean prior to treatment was 120.5ng/ml. At one month levels were 80.7ng/ml (30.7% decrease), and three months levels were 76.8ng/mL. (37.1% decrease).

Keller, D. Systemic LpPLA2 cardiovascular marker response to direct medication delivery periodontal treatment. Cardiovascular System. December 2014. ISSN 2052-4358.

PerioProtect Method lowers Lp-PLA2

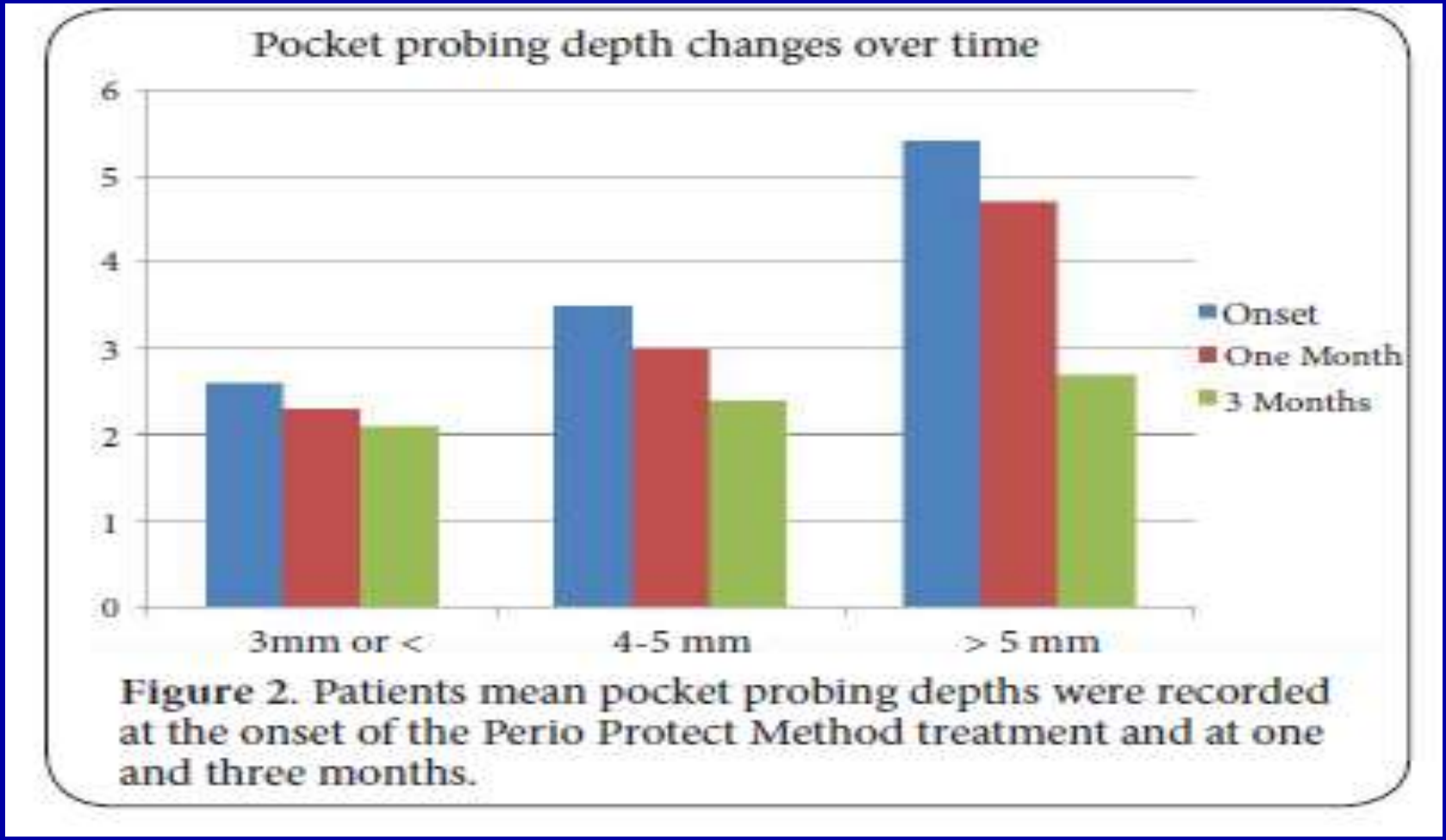


Figure 2. Patients mean pocket probing depths were recorded at the onset of the Perio Protect Method treatment and at one and three months.

Keller, D. Systemic LpPLA2 cardiovascular marker response to direct medication delivery periodontal treatment. Cardiovascular System. December 2014. ISSN, 2052-4358.

PerioProtect Method lowers Lp-PLA2

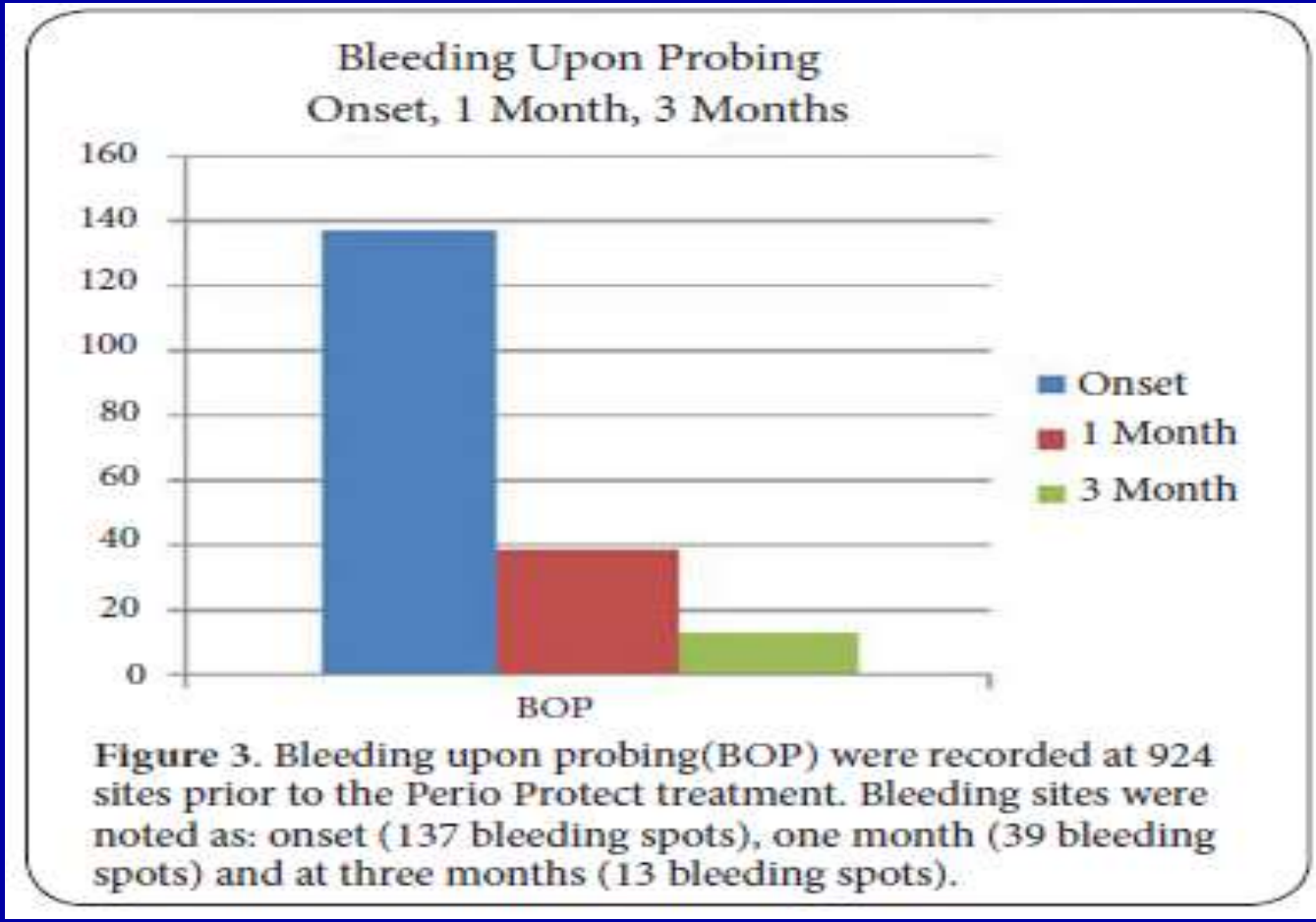


Figure 3. Bleeding upon probing(BOP) were recorded at 924 sites prior to the Perio Protect treatment. Bleeding sites were noted as: onset (137 bleeding spots), one month (39 bleeding spots) and at three months (13 bleeding spots).

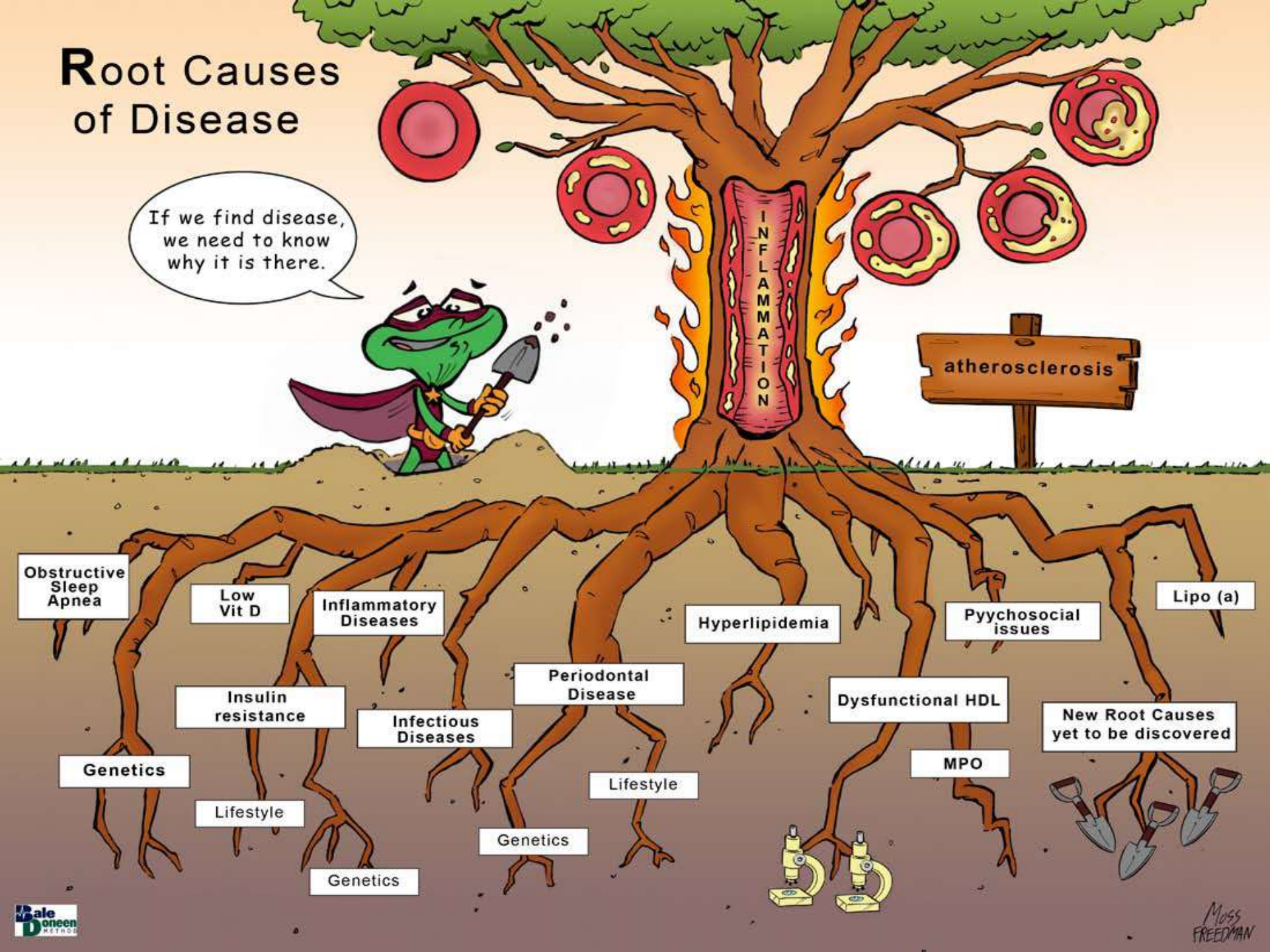
Keller, D. Systemic LpPLA2 cardiovascular marker response to direct medication delivery periodontal treatment. Cardiovascular System. December 2014. ISSN, 2052-4358.

PerioProtect Method lowers Lp-PLA2

Bale/Doneen Take-Away:

1. Although this was a small pilot study, it does show that the PerioProtect method lowers Lp-PLA2 levels.
2. Confounders were not reported.
3. This is an opportunity to broaden Dr. Keller's research to larger data sets – working together with medical and dental to provide optimal health to the patients.
4. The PerioProtect trays can be promoted in medical and dental practices.

Keller, D. Systemic LpPLA2 cardiovascular marker response to direct medication delivery periodontal treatment. Cardiovascular System. December 2014. ISSN, 2052-4358.


Root Causes of Disease
If we find disease, we need to know why it is there.
INFLAMMATION
atherosclerosis
Obstructive Sleep Apnea
Low Vit D
Inflammatory Diseases
Hyperlipidemia
Pyychosocial issues
Lipo (a)
Insulin resistance
Periodontal Disease
Dysfunctional HDL
New Root Causes yet to be discovered
Infectious Diseases
Genetics
Lifestyle
MPO
Genetics
Lifestyle
Genetics
Genetics
Dale Boneen METHOD
MOSS FREEDMAN

Diastolic Blood Pressure: Optimal Care

DBP < 70 mmHg shows increased CVD risk

Framingham Heart Study

1948: 5200 men & women, age 30-62

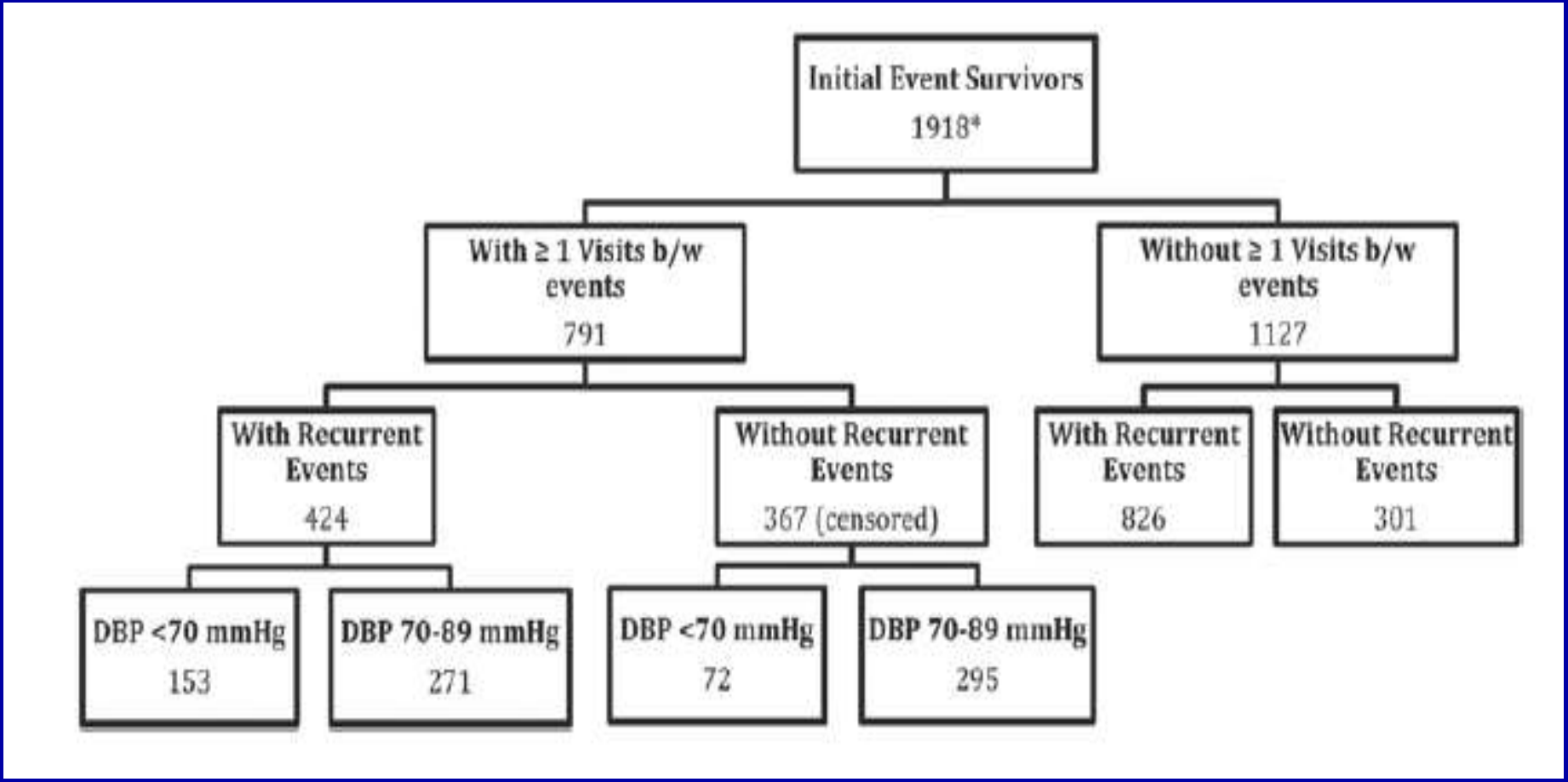
1971: 5124 men & women who were children and spouses of original group.

Offspring cohort – repeated exam every 4 years.

Now: inclusion criteria for this analysis results in: 791 initial hypertensive CVD event survivors with ≥1 visit.

Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

DBP < 70 mmHg shows increased CVD risk



Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

DBP < 70 mmHg shows increased CVD risk

Bivariate Analysis – of 791 hypertensive participants (mean age 75 years, female 47%), who survived their initial CVD event, 225 (28%) had DBP <70 mmHg and 566 (72%) had DBP 70-89 mmHg

DBP <70 mmHg – 153/225 (68%) had CVD event

DBP 70-89 mmHg – 271/566 (48%) had CVD event.

Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

DBP < 70 mmHg shows increased CVD risk

Table 2. Cox Regressions for Combined CVD Events: Treated and Untreated

Total CVD	χ^2	*P* Value	HR	95% CI
Unadjusted				
DBP <70 vs 70–89 mm Hg	238.4	<0.0001	5.9	4.7–7.4
Age- and sex-adjusted				
DBP <70 vs 70–89 mm Hg	190.8	<0.0001	5.7	4.5–7.3
Age (per SD)	4.3	0.0373	1.0	1.0–1.0
Sex (male vs female)	7.5	0.0063	0.7	0.6–0.9
Fully adjusted*				
DBP <70 vs 70–89 mm Hg	189.6	<0.0001	5.9	4.6–7.5
Age (per SD)	9.1	0.0026	1.2	1.1–1.4
Sex (male vs female)	10.8	0.001	0.7	0.6 –0.9
BMI (per SD)	0.016	0.898	0.99	0.9 –1.1
Total cholesterol (per SD)	10.0	0.0016	1.2	1.1 –1.3
Smoking (current vs other)	0.8	0.3701	1.1	0.9–1.4
Diabetes mellitus (yes vs no)	14.1	0.0002	1.7	1.3–2.2

BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; and HR, hazard ratio.
*Adjusted for age per SD, sex (male vs female), BMI (per SD), total cholesterol (per SD), smoking (yes vs no), and diabetes mellitus (yes vs no).

Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

DBP < 70 mmHg shows increased CVD risk

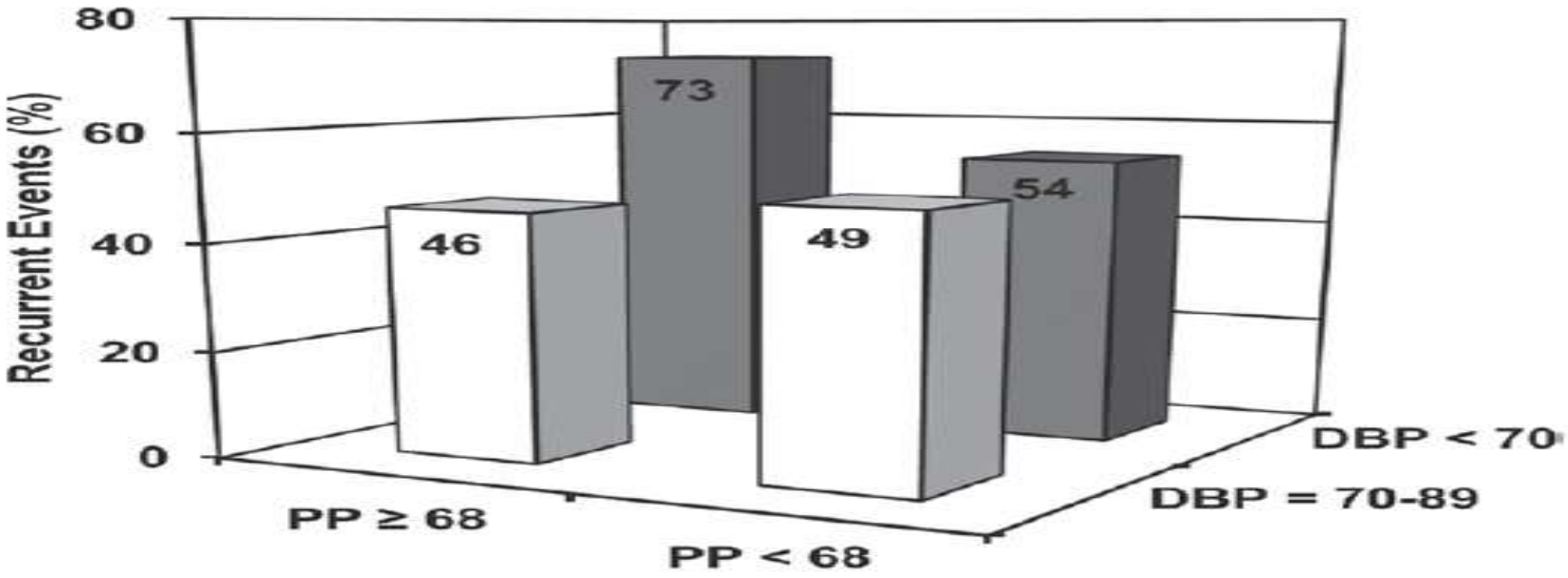


Figure 3. Bar graph depicts the 4 possible binary combinations of median pulse pressure cut points (≥68 vs <68 mm Hg) and diastolic blood pressure (DBP) cut points (<70 vs 70–89 mm Hg) that predicted recurrent cardiovascular disease (CVD) risk in the 791 initial CVD event survivors with ≥1 office visits. The highest event rate occurred in individuals with DBP <70 mm Hg and pulse pressures of ≥68 mm Hg that predicted CVD events significantly. (P<0.0001 across the 4 DBP×pulse pressure groupings; χ^2=32.6). No other binary paring of pulse pressure and DBP showed significant prediction of CVD events.

Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

DBP < 70 mmHg shows increased CVD risk

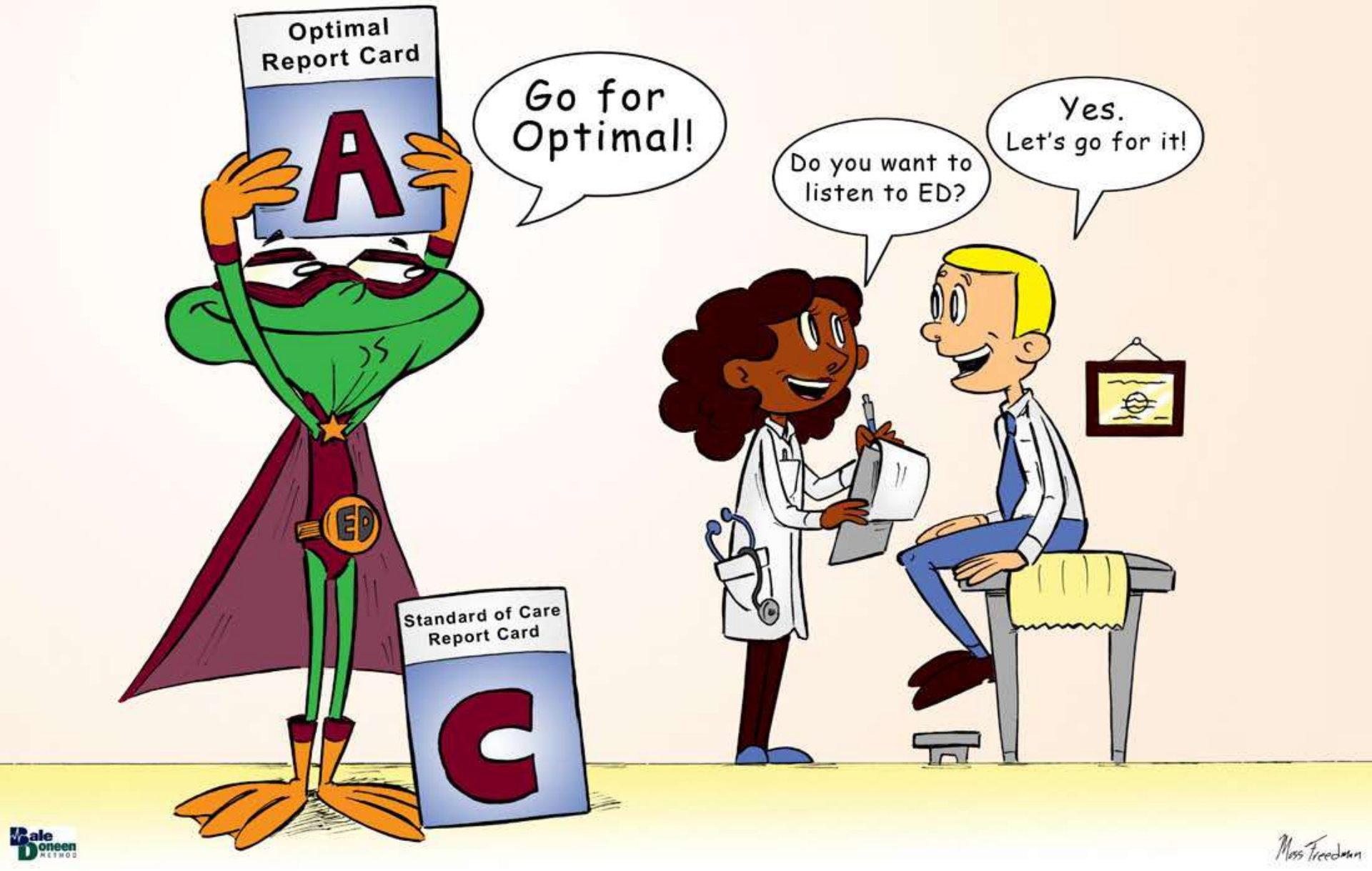
Bale/Doneen Take-Away:

Anti-hypertensive therapy for patients >70 years old with ischemic heart disease should preferentially decrease SBP over DBP, lower pulse pressure, decrease arterial stiffness, improve oxygen supply/demand to the left ventricle – providing protection against ischemic.

Watch DBP <70 and pulse pressures ≥ 68

Franklin, S, Gokhale, S., Chow, V., et al. Does Low DBP contribute to the risk of recurrent hypertensive Cardiovascular disease events? Hypertension. 2015; 65:00-00.

Optimal vs Standard of Care



Total Bilirubin and CAD risk

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

Bilirubin, an end product of heme metabolism, has demonstrated to be an endogenous antioxidant. Proposed antioxidative properties – likely mediated by efficient scavenging of peroxyl radicals and inhibition of the oxidation of LDL.

Ansung-Ansan cohort study – Baseline exams performed in 2001 and 2002, with f/u exams have been carried out every 2 years since. Present study involved 4 year follow-up. Total of 8,593 subjects – 0.9% newly developed CAD events during the 4 years of follow-up. Age 40-69 years.

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

Subjects with serum bilirubin levels < 0.32 mg/dl were found to have a higher risk for future CAD events than all other subjects.

HR 2.102, 95% CI, 1.237 to 3.570, p=0.006

After adjustment for age, gender, BMI, Triglycerides, GGT, hsCRP, DM and HTN, subjects with serum Bilirubin <0.32 remained at increased CV risk.

HR 1.890, 95% CI, 1.088 to 3.284, p=0.024)

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

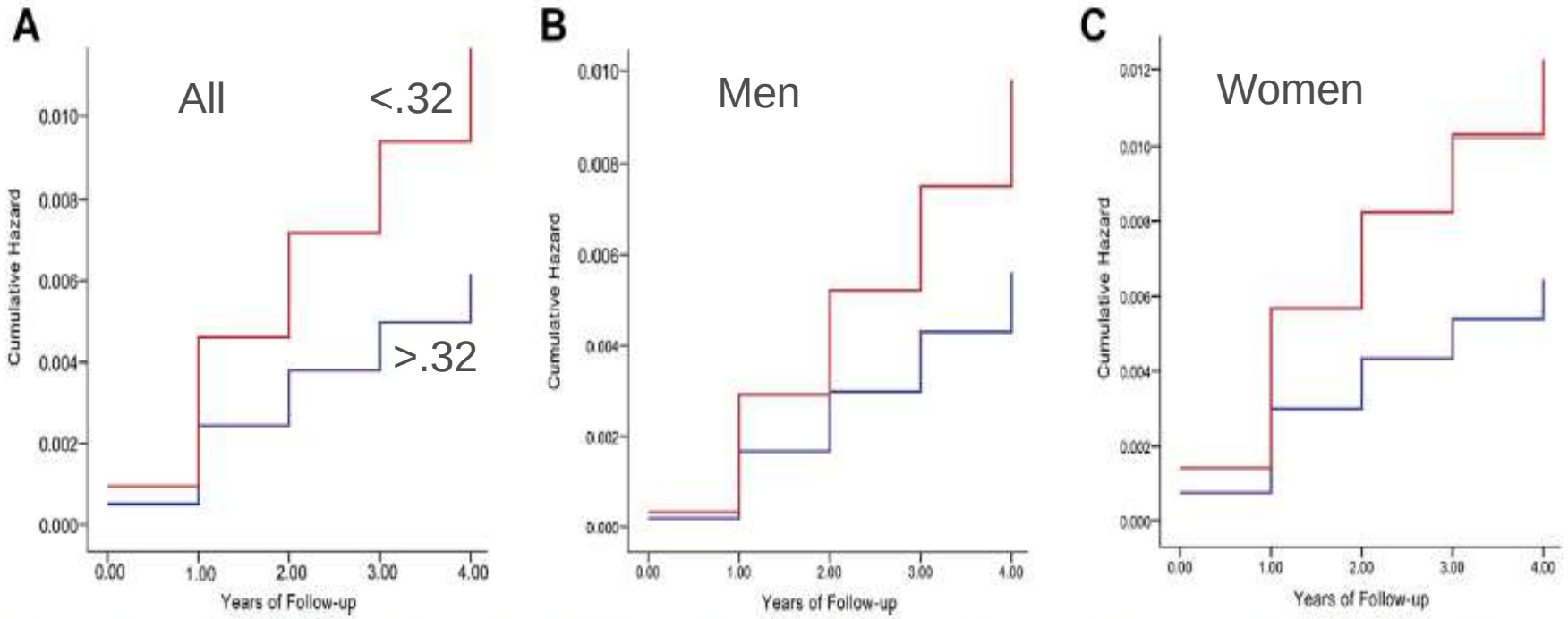


Figure 1. Comparison of CAD risk according to serum bilirubin levels. Hazard function by Cox proportional-hazards regression for CAD events according to serum bilirubin levels (cutoff 0.32 mg/dl), adjusted for age, gender, body mass index, triglyceride, γ-glutamyl transferase, C-reactive protein, diabetes mellitus, and hypertension in *(A)* the entire population, *(B)* men, and *(C)* women. *Red line*: subjects with serum bilirubin levels ≤0.32 mg/dl; *blue line*: subjects with serum bilirubin levels >0.32 mg/dl.

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

Hazard ratios (HR) of incident coronary artery disease events according to metabolic syndrome and bilirubin level during 4 years of follow-up

	Total		MS		No MS	
	HR (95%CI)	P	HR (95% CI)	P	HR (95% CI)	P
Bili >.32mg/dl, no MS	1	-	-	-	1	-
Bili <.32mg/dl, no MS	1.774 (0.669–4.704)	0.250	-	-	1.774 (0.669–4.704)	.249
Bili >.32mg/dl, + MS	3.089 (1.803–5.290)	<0.001	1	-	-	-
Bili <.32mg/dl, + MS	6.228 (3.118–12.437)	<0.001	2.016 (1.069–3.800)	0.030	-	-

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

Subjects with metabolic Syndrome 3,156 (36.7%) found to have a higher risk of future CAD events than subjects without metabolic syndrome

HR 3.366, 95% CI 2.079 to 5.448, p <0.001

Subjects with Met Synd and Bilirubin <0.32mg/dl:

HR 6.228, 95% CI 3.118 to 12.437, p<0.001

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

Ways to raise bilirubin

- Exercise
- Lower BMI
- Testosterone*
- Nonsmoking status
- Niacin via stimulating heme oxygenase activity
- Statins increase bilirubin 10 to 20%
- Antihypertensives ??
- Treating seasonal affective disorder^

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

*Wang, C. (2004). *Journal of Clinical Endocrinology & Metabolism, 89*(5), 2085-2098.

^Kurlansik, S. L., & Ibay, A. D. (2012). *Am Fam Physician, 86*(11), 1037-1041.

Low Total Bilirubin Levels (<0.32 mg/dl) on risk of CAD in patients with metabolic syndrome

Bale/Doneen Take-Away:

1. Measure total serum bilirubin on all patients
2. Patient with metabolic syndrome and a bilirubin level < 0.32 mg/dl carries a 6 times higher risk for CAD.
3. Bilirubin is endogenous and anti-inflammatory
4. Bilirubin is inversely related to CAD risk.

Song, Yl, Koo, B., Cho, N, Moon, M. Effect of low serum total bilirubin levels on risk of coronary artery disease in patients with metabolic syndrome. Am J Cardiol 2014:114:1695-1700.

NT-ProBNP and predictability of heart failure in women

NT-ProBNP adds predictability to risk assessment for women

Prospective case-cohort within the WHI observation study, selected 1821 incident cases of CVD (746 MI, 754 ischemic strokes, 160 hemorrhagic strokes, and 161 other CV deaths) and randomly selected reference cohort of 1,992 women without CVD at baseline.

Determine if NT-ProBNP adds predictability

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

TABLE 2 Association of NT-proBNP With Incident CVD

	Hazard Ratio (95% CI) by Quartile of NT-proBNP						
	Quartile 1 <50.9 ng/l	Quartile 2 50.9-<82.7 ng/l	Quartile 3 82.7-<140.8 ng/l	Quartile 4 ≥140.8 ng/l	p Value for Trend	Hazard Ratio (95% CI) per 1-SD* Unit Increase in Ln-NT-proBNP	p Value
Age and race/ethnicity adjusted	1.00	0.91 (0.72-1.14)	1.18 (0.95-1.45)	1.55 (1.26-1.92)	<0.0001	1.36 (1.26-1.48)	<0.0001
MV adjusted†	1.00	0.93 (0.74-1.17)	1.28 (1.03-1.59)	1.62 (1.30-2.02)	<0.0001	1.39 (1.28-1.51)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.92 (0.71-1.17)	1.29 (1.02-1.63)	1.53 (1.21-1.94)	<0.0001	1.37 (1.25-1.49)	<0.0001
MV + RRS adjusted§	1.00	0.94 (0.73-1.21)	1.29 (1.01-1.64)	1.53 (1.20-1.95)	<0.0001	1.36 (1.24-1.49)	<0.0001

*The SD of natural logarithm transformed NT-proBNP is 0.838. †Multivariable (MV)-adjusted model is adjusted for age and race/ethnicity, prior diabetes, angina, statin use, and current and past hormone therapy. ‡MV + traditional risk factor model is adjusted for the covariables in the MV model, plus current smoking and the natural logs of systolic blood pressure, total and HDL cholesterol, and blood pressure treatment. §MV + Reynolds Risk Score (RRS) model: adjusted for the covariables in the MV model, plus current smoking, the natural logs of systolic blood pressure, total and HDL cholesterol, hsCRP, family history of premature MI, and HbA1c among women with diabetes.

CI = confidence interval; Ln = Ln-transformed; other abbreviations as in Table 1.

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

TABLE 3 Association of NT-proBNP With Cardiovascular Mortality, Incident Fatal and Nonfatal MI, and Incident Fatal and Nonfatal Stroke

	Hazard Ratio (95% CI) by Quartile of NT-proBNP					Hazard Ratio (95% CI) per	
	Quartile 1 <50.9 ng/l	Quartile 2 50.9-<82.7 ng/l	Quartile 3 82.7-<140.8 ng/l	Quartile 4 ≥140.8 ng/l	p Value for Trend	1-SD* Unit Increase in Ln-NT-proBNP	p Value
Cardiovascular mortality							
MV adjusted†	1.00	0.84 (0.42-1.68)	1.79 (0.99-3.24)	2.95 (1.67-5.20)	<0.0001	1.95 (1.65-2.31)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.81 (0.40-1.62)	1.78 (0.98-3.26)	2.82 (1.57-5.05)	<0.0001	1.89 (1.59-2.26)	<0.0001
MV + RRS adjusted§	1.00	0.82 (0.41-1.66)	1.81 (0.99-3.32)	2.66 (1.48-4.81)	<0.0001	1.80 (1.51-2.14)	<0.0001

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

TABLE 3 Association of NT-proBNP With Cardiovascular Mortality, Incident Fatal and Nonfatal MI, and Incident Fatal and Nonfatal Stroke

	Hazard Ratio (95% CI) by Quartile of NT-proBNP					Hazard Ratio (95% CI) per 1-SD* Unit Increase in Ln-NT-proBNP	
	Quartile 1 <50.9 ng/l	Quartile 2 50.9-<82.7 ng/l	Quartile 3 82.7-<140.8 ng/l	Quartile 4 ≥140.8 ng/l	p Value for Trend		p Value
Stroke (fatal and nonfatal)							
MV adjusted†	1.00	0.95 (0.72-1.25)	1.21 (0.93-1.57)	1.72 (1.33-2.22)	<0.0001	1.40 (1.28-1.53)	<0.0001
MV + traditional risk factor adjusted‡	1.00	0.93 (0.70-1.25)	1.22 (0.93-1.61)	1.60 (1.21-2.09)	<0.0001	1.35 (1.22-1.48)	<0.0001
MV + RRS adjusted§	1.00	0.95 (0.71-1.27)	1.21 (0.92-1.60)	1.60 (1.22-2.11)	<0.0001	1.34 (1.22-1.48)	<0.0001

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

TABLE 4 Changes to 10-Year CVD Risk Prediction Statistics After Adding NT-proBNP to Existing Risk Prediction Models

	MV + Traditional Risk Factor Covariables			RRS Covariables		
	MV + Traditional Risk Factor	MV + Traditional Risk Factor + NT-proBNP	p Value*	RRS	RRS + NT-proBNP	p Value†
C-statistic	0.770 (0.760-0.779)	0.779 (0.769-0.789)	0.0004	0.768 (0.757-0.776)	0.776 (0.765-0.785)	0.0001
Net reclassification improvement	–	0.059 (0.030-0.089)	<0.0001	–	0.033 (0.002-0.062)	0.03
Category-less net reclassification improvement	–	0.103 (0.020-0.183)	0.02	–	0.097 (0.013-0.19)	0.03
Integrated discrimination improvement	–	0.0102 (0.0055-0.016)	0.0001	–	0.0080 (0.0039-0.012)	0.0002

Values in parentheses are 95% CI. *Comparison of the performance of MV + traditional risk factor covariables + NT-proBNP concentrations versus MV + traditional risk factor covariables without NT-proBNP concentrations. The MV and traditional risk factor covariables were age, race/ethnicity, prior diabetes, angina, statin use, current or past hormone therapy, current smoking, and the natural logs of systolic blood pressure, total and HDL cholesterol, and blood pressure treatment. †Comparison of the performance of RRS covariables + NT-proBNP concentrations to RRS performance without NT-proBNP concentrations. The RRS covariables were age, race/ethnicity, current smoking, the natural logs of systolic blood pressure and total and HDL cholesterol, hsCRP, family history of premature MI, and HbA1c among women with diabetes.

Abbreviations as in Tables 1 and 2.

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

NT-proBNP were higher at study entry among incidence cases (120.3 ng/l) than among control subjects (100.4 ng/l) – p <0.0001

Women in highest quartile of NT-ProBNP (>140.8ng/l) were at 53% increased risk of CVD verses those in the lowest quartile after adjustments of traditional risk factors p <0.0001)

Similar associations for:

RRS – 1.53 (95% CI, 1.20-1.95, p<0.0001)
CV Death – 2.66 (95% CI, 1.48-4.81, p<0.0001)
MI – 1.39 (95% CI, 1.02-1.88, p=0.008)
stroke – 1.60(95% CI, 1.22-2.11, p<0.0001)

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

NT-ProBNP adds predictability to risk assessment for women

Bale/Doneen Take-Away:

NT-ProBNP is VERY relevant for women and does add independent predictive value on top of all other risk analyses.

Remember: Optimal care for n of 1.

Everett et al. NT-ProBNP and CVD in Women. JACC vol. 64 Nov 17, 2014. 1989-97.

Genetics

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med
Volume 371(22):2072-2082
November 27, 2014

Inactivating Mutations of NPC1L1 and Protection from Coronary Heart Disease

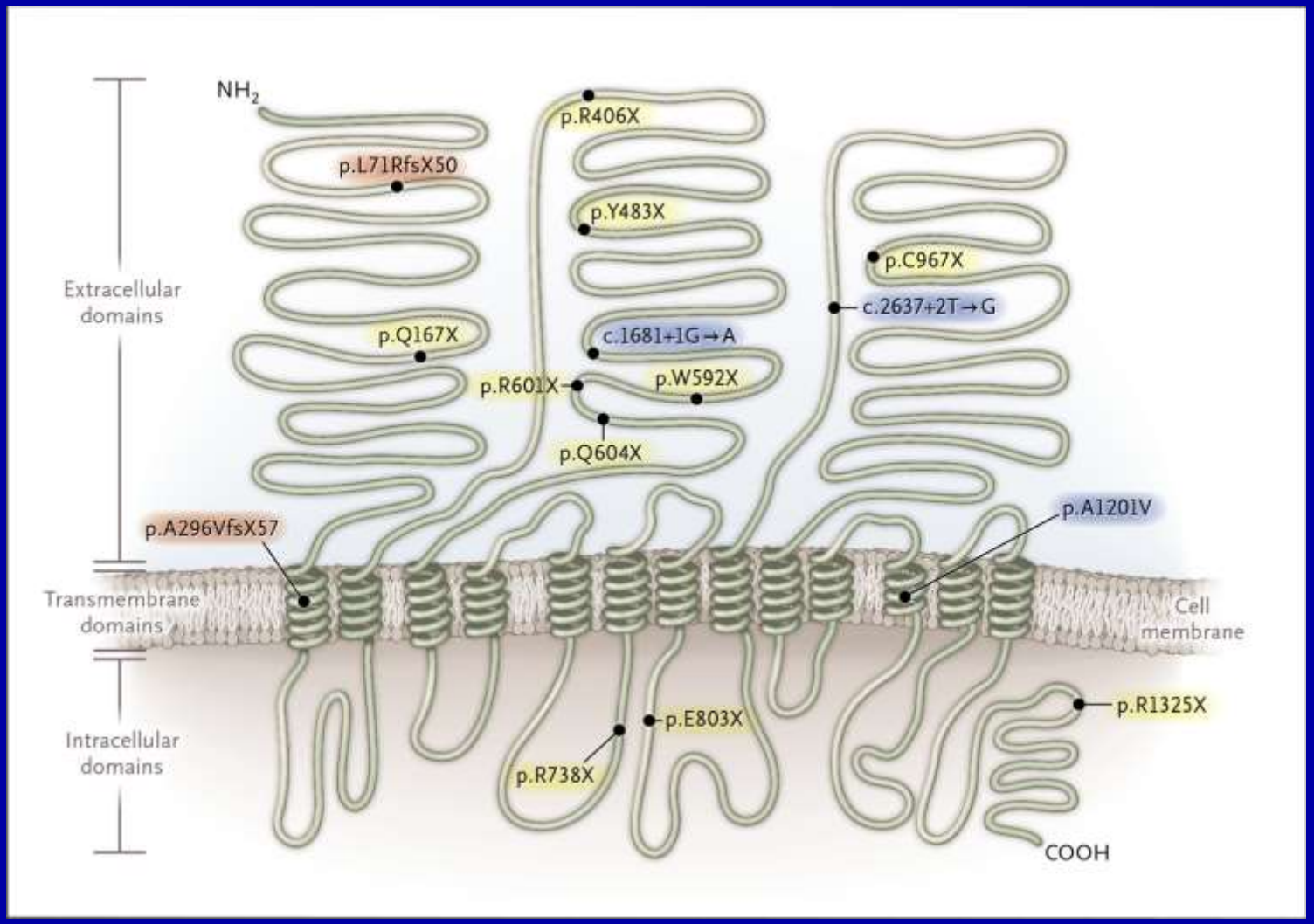
- Sequenced exons of NPC1L1 in 7346 patients with coronary heart disease and 14,728 controls.

- Mutation carriers had lower LDL cholesterol levels and a lower risk of coronary heart disease than did noncarriers.

- Identified 15 distinct NPC1L1 inactivating mutations; approximately 1 in every 650 persons was a heterozygous carrier for 1 of these mutations.

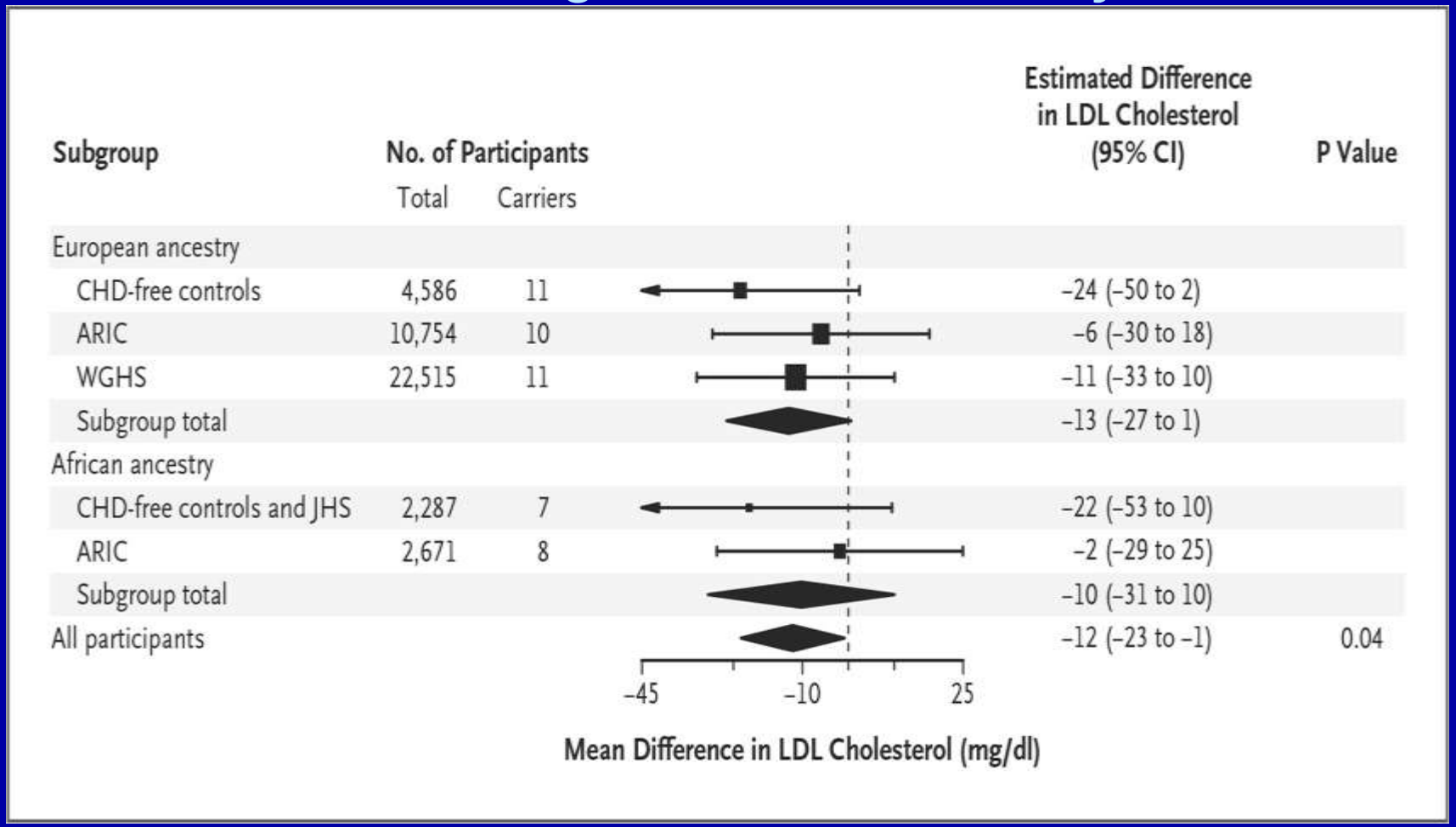
N Engl J Med, Volume 371(22):2072-2082. November 27, 2014

Inactivating Mutations in *NPC1L1* Identified in the Study.



The Myocardial Infarction Genetics Consortium Investigators. N Engl J Med 2014;371:2072-2082

Association between the Presence of Inactivating Mutations in *NPC1L1* and LDL Cholesterol Levels, According to Genetic Ancestry.



The Myocardial Infarction Genetics Consortium Investigators. N Engl J Med 2014;371:2072-2082

Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.

Table 2. Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.*

Variable	Mean Difference between Carriers and Noncarriers*	P Value
Cholesterol (mg/dl)		
Total	−13	0.03
Low-density lipoprotein	−12	0.04
High-density lipoprotein	2	0.29
Triglycerides (% change)	−12	0.11†

* The mean difference is the summary effect estimate for carriers of inactivating mutations in *NPC1L1*, as compared with noncarriers, after adjustment for age, sex, and study. Participants from population-based studies (ARIC, JHS, and WGHS) and controls without coronary heart disease from case–control studies were included in this analysis. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† This P value was calculated with the use of natural log transformation of the values.

The Myocardial Infarction Genetics Consortium Investigators. N Engl J Med 2014;371:2072-2082

Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.

- Carrier status was associated with a relative reduction of 53% in the risk of coronary heart disease (OR for carriers 0.47; 95% CI, 0.25 to 0.87; p=0.008).

- Only 11 of the 29,954 patients with coronary heart disease had an inactivating mutation (carrier frequency, 0.04%) in contrast to 71 of 83,140 controls (carrier frequency, 0.09%).

- Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease. No inflammatory associations were evaluated.

The Myocardial Infarction Genetics Consortium Investigators. N Engl J Med 2014;371:2072-2082

Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.

Bale/Doneen Take-Away:

Genetics are always of interest when identifying who might be at lower or higher CVD risk.

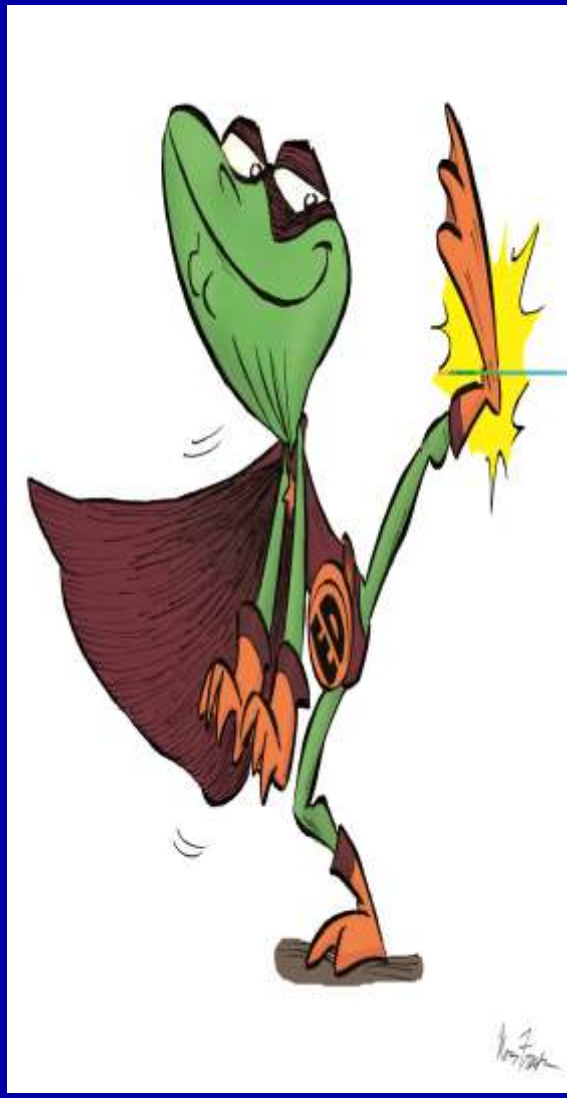
It will be interesting to see a genetic overlay on various study sets to see if people who are carriers/noncarriers respond differently to various treatments.

The 53% event reduction for the inactivating carriers of NPC1L1, exceed any anticipated risk reduction explained from the lipid differences.

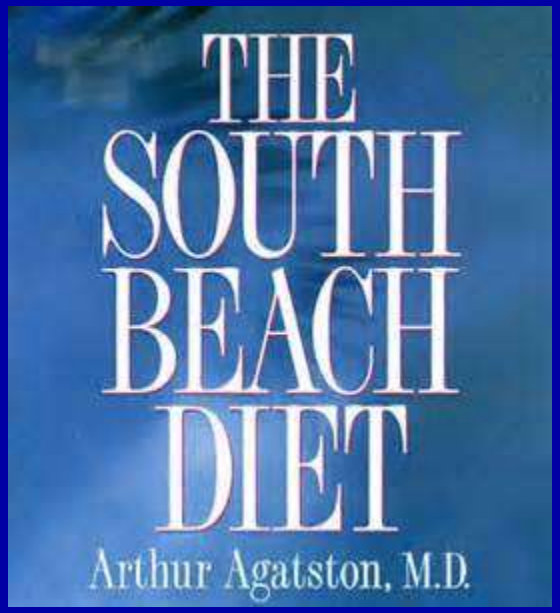
The Myocardial Infarction Genetics Consortium Investigators. N Engl J Med 2014;371:2072-2082

EDFROG IRA

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



4 popular diets – weight loss and CVD risk factors



Long-term effects of 4 popular diets on weight loss and CVD risk factors.

Systemic review to examine efficacy of:

- Atkins
- South Beach
- Weight Watchers (WW)
- Zone Diet

Outcome: sustained weight loss and CV risk factors at ≥ 12 months

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Long-term effects of 4 popular diets on weight loss and CVD risk factors.

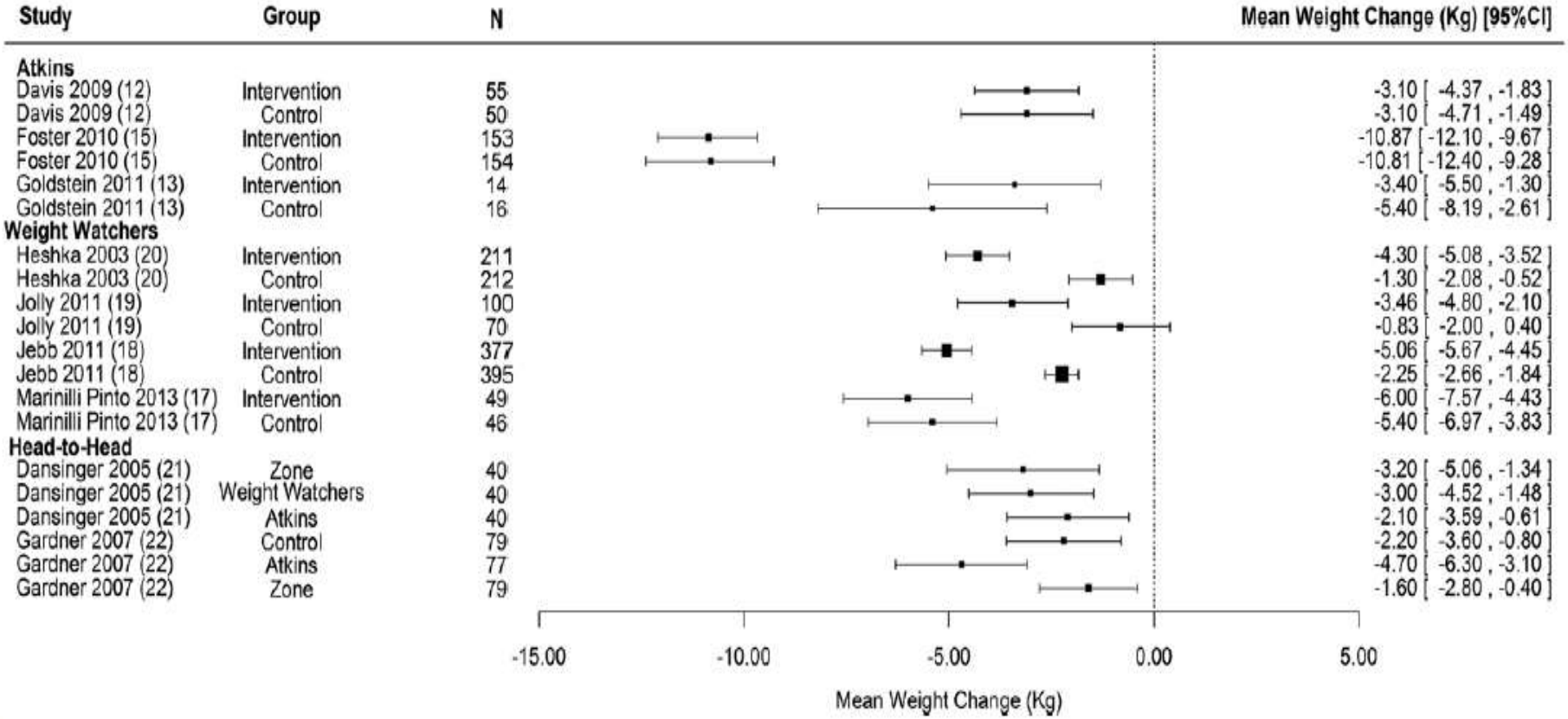


Figure 3. Forest plot for mean weight change from baseline to 12 months among long-term trials. N is the number of patients included in the 12-month analysis. CI indicates confidence interval.

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Long-term effects of 4 popular diets on weight loss and CVD risk factors.

Head-to-head weight loss at 12 months

- Atkins: -2.1 to -4.7 kg
- Weight Watchers: -3.0 kg
- Zone: -1.6 to -3.2 kg
- Control: -2.2 kg

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Long-term effects of 4 popular diets on weight loss and CVD risk factors.

Lack of control for ALL CVD risk factors:

Lipids

Atkins – adverse effect on LDL with potential improved HDL

WW and SB – no or limited data

2 RCTs head-to-head: no difference b/t Atkins, WW & Zone

Blood Pressure

Atkins & WW had favorable effecs on SBP and DBP

No BP data available on SB and limited with Zone

Glycemic Control Measures

No major differences between the diets on glycemic measures.

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Long-term effects of 4 popular diets on weight loss and CVD risk factors.

Only Weight Watchers was consistently more efficacious at reducing weight (range of mean change -3.5 to -6.0 kg versus -0.8 to -5.4 kg, p=<0.05) for 3 of 4 RCTs

At 24 months, data suggest that weight loss with WW or Atkins was partially regained over time.

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Long-term effects of 4 popular diets on weight loss and CVD risk factors.

Bale/Doneen Take-Away:

1. RCT meta-analyses can be limiting to draw independent conclusions.
2. All 4 diets were modestly effective for short term weight loss but benefits are not sustainable long-term
3. WW was better at 12 months than Atkins and SB and was only diet to achieve consistent weight loss across trials.
4. Remain grounded in a genetically based (ApoE) diet plan for CVD risk – Remember Optimal (individualized) care is always best!
5. Inflammation was not addressed – skinny people have heart attacks and strokes everyday ☺

Atallah, R, Filion, K, Wakil, S, et al. Long term effects of 4 popular diets on weight loss and cardiovascular risk factors. Circ Cardiovasc Qual Outcomes. 2014;7:00-00.

Beetroot juice and BP reduction

Dietary Nitrate lowers blood pressure

68 patients with hypertension in a double-blind, placebo-controlled trial to receive daily dietary supplement for 4 weeks with either dietary nitrate (250ml daily of beetroot juice) or a placebo (250ml daily of nitrate free beetroot juice)

Primary endpoint: change in clinic, ambulatory and home BP compared with placebo.

Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

Dietary Nitrate lowers blood pressure

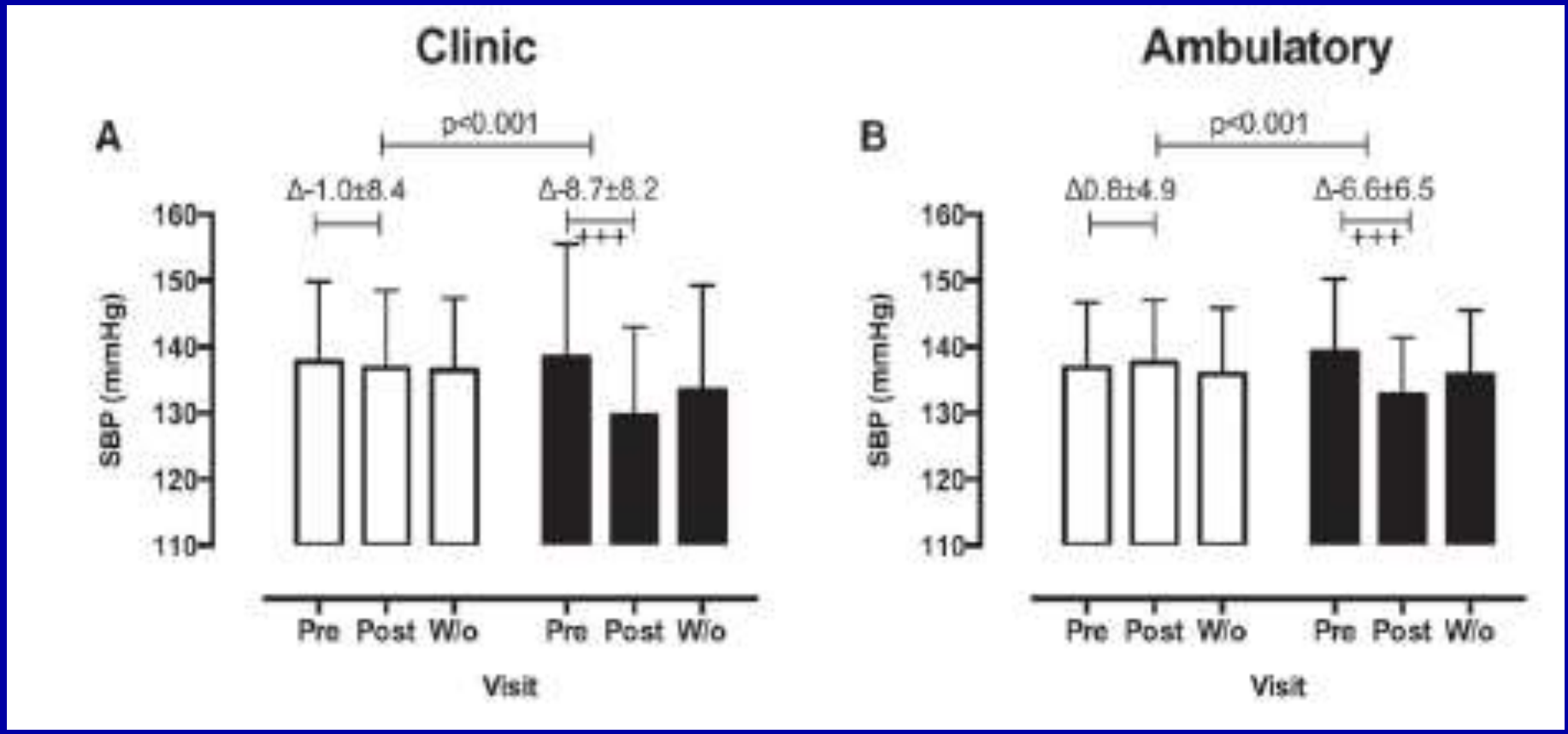
Table. Baseline Characteristics Stratified by Treatment Allocation

Treatment Allocation	Placebo	Dietary Nitrate	Significance
Demographics			
n (female)	32 (22)	32 (16)	0.14
Age, y	56.3±16.4	57.6±13.9	0.73
BMI, kg/m²	26.5±4.0	26.8±5.0	0.74
Medications			
Hypertension drugs	1.0±1.2	1.0±1.2	0.84
Patients on (n)			
ACE-I/ARB	10	11	
β-Blocker	3	3	
CCB	14	10	
Diuretic	5	4	
α-Blocker	2	4	
Aldosterone antagonist	1	1	
Statins	3	4	
Antiplatelet drugs	0	0	
Screening ABP, mm Hg			
SBP	148.2±10.0	149.0±11.0	0.73
DBP	88.2±8.0	88.9±9.8	0.75
HR	70.6±8.3	72.9±10.7	0.32
Biochemistry			
eGFR, mL/min	79.1±16.3	85.0±16.6	0.17
Total cholesterol: HDL-C ratio	3.4±1.3	3.1±0.7	0.37

Data are presented as mean±SD. Significance shown in the last column for unpaired Student *t* test, except for analysis of sex for which Fisher exact test was performed. ABP indicates ambulatory blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; and SBP, systolic blood pressure.

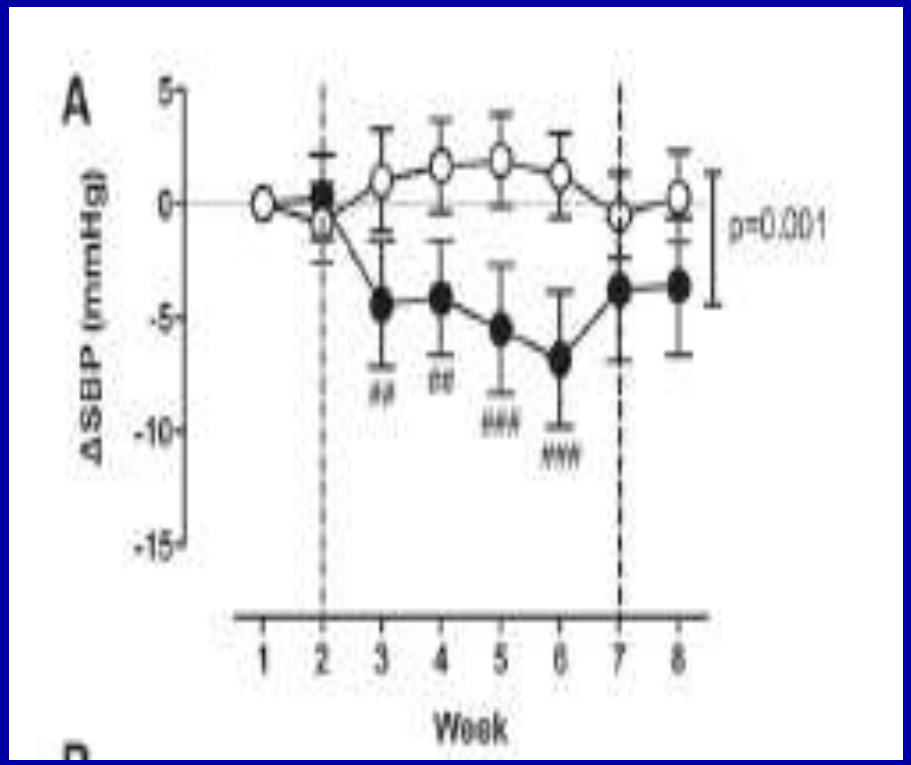
Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

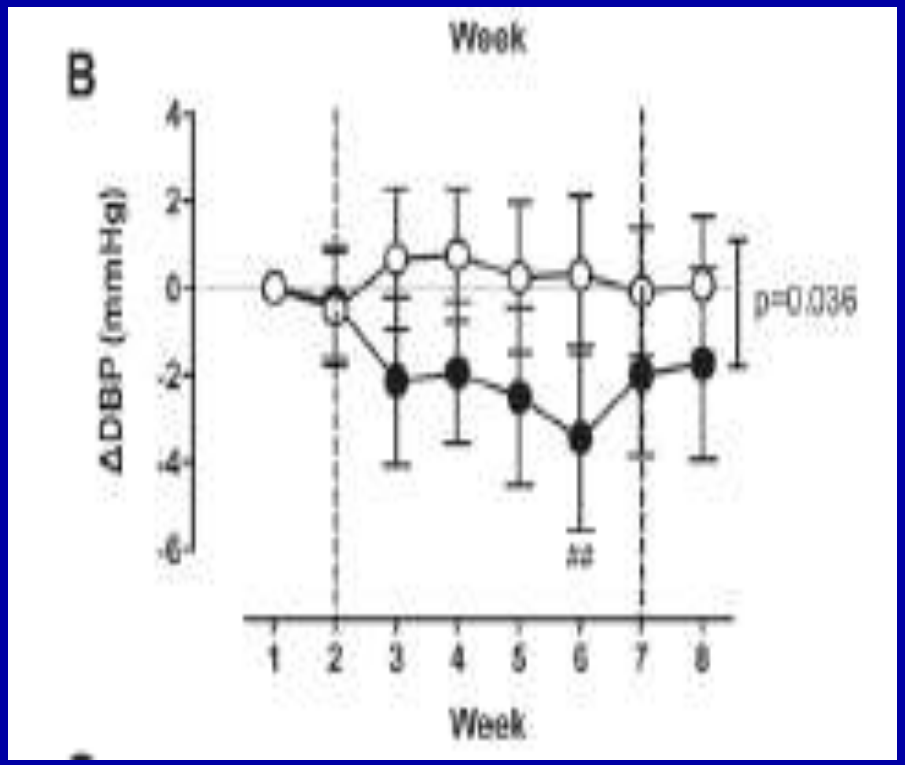
Dietary Nitrate lowers blood pressure



Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

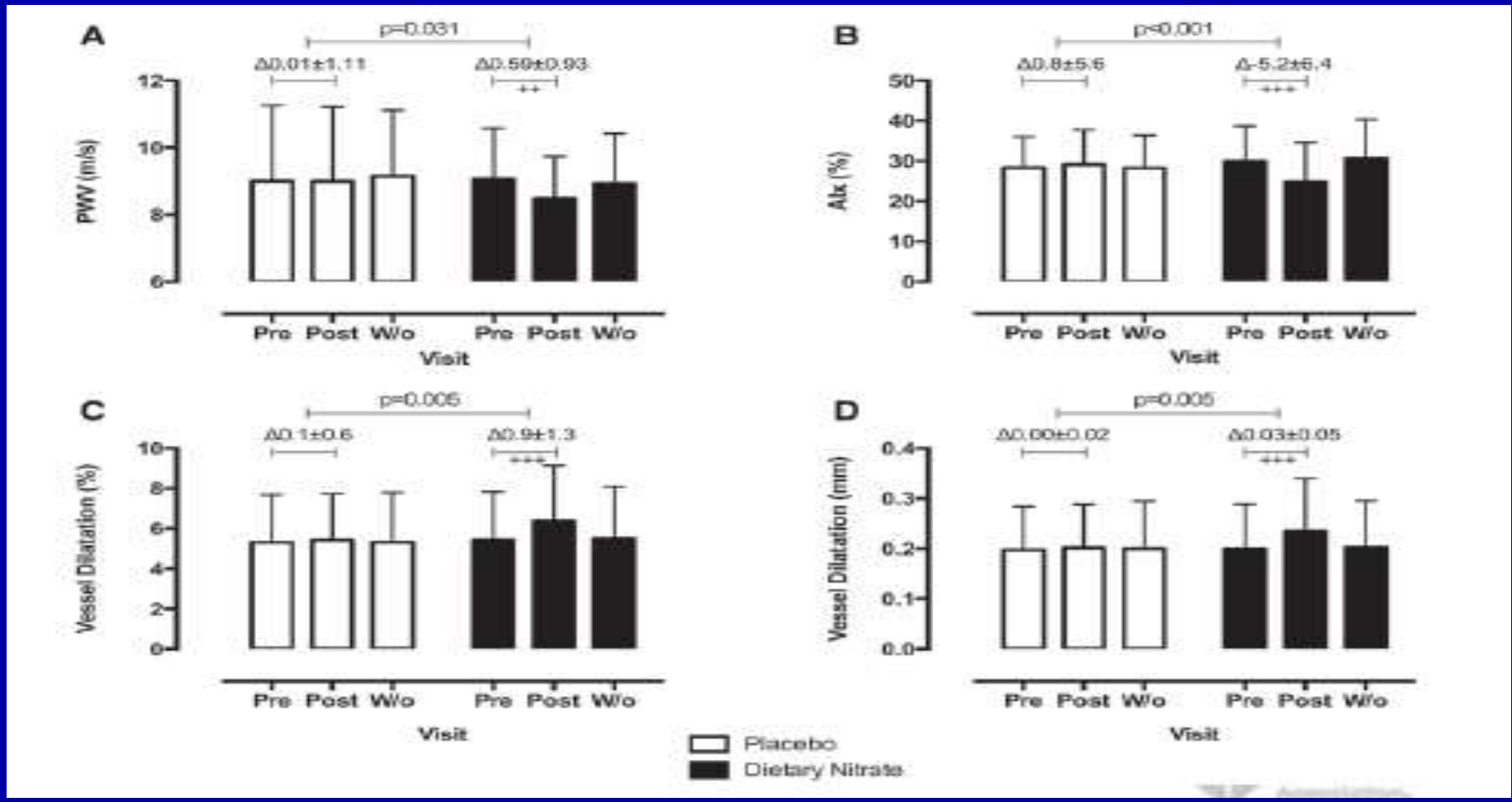
Dietary Nitrate lowers blood pressure Home BP readings over 4 weeks:





Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

Dietary Nitrate lowers blood pressure Pulse Wave Velocity & Vessel Dilatation.



Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

Dietary Nitrate lowers blood pressure Pulse Wave Velocity & Vessel Dilatation.

Dietary nitrate (250ml beet juice daily) associated with reduction in BP:

Clinic: Mean **reduction in BP was 7.7/2.4 mmHg**

(95% CI; 3.6-11.8/0.0-4.9, p=<.0001 and p=0.050)

24 hr BP: Mean **reduction in BP was 7.7/5.2 mmHg**

(95% CI; 4.1-11.2/2.7-7.7, p<0.001 for both)

Home BP: Mean **reduction in BP was 8.1/3.8 mmHg**

(95% CI; 3.8-12.4/0.7-6.9, p<0.001 and p<0.01)

Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

Dietary Nitrate lowers blood pressure Pulse Wave Velocity & Vessel Dilatation.

Dietary nitrate (250ml beet juice daily) associated with improvement in endothelial function and arterial stiffness:

Pulse Wave Velocity (arterial stiffness) :

Reduced by 0.59 m/s (0.24-0.93; $p<0.01$)

Flow Mediated Dilitation (endothelial function):

Improved by average of 20% ($p<0.0001$)

Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

Dietary Nitrate lowers blood pressure Pulse Wave Velocity & Vessel Dilatation.

Bale/Doneen Take-Away:

Beet Juice is a safe and effective tool to lower Blood Pressure and improve arterial wall health.

Kapil, V., Khambata, R., Robertson, A., et al. Dietary Nitrate provides sustained blood pressure lowering in hypertensive patients. Hypertension. Dec. 2015;65:00-00

IMPROVE -IT

VS

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

National Lead Investigators and Steering Committee (1158 sites, 39 Countries)

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Harvey White
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Terje Pedersen
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Manuel Carrageta
Portugal (102)

Ki-Bae Seung
S. Korea (118)

Tibor Duris
Slovakia (121)

Anthony Dalby
S. Africa (186)

Jose Lopez-Sendon
Spain (551)

Mikael Dellborg
Sweden (480)

Francois Mach
Switzerland (263)

Sema Guneri
Turkey (50)

Alexander Parkhomenko
Ukraine (159)

Adrian Brady
United Kingdom (318)

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Christie Ballantyne*
James de Lemos*
Neal Kleiman*
Darren McGuire*
United States (5869)

Singapore (75), Malaysia (59), Hong Kong (58) Ecuador (45), Taiwan (46)

**Steering Comm Member, [1] Deceased, [2] 2005–2013*

Dale Doneen METHOD

Goals of IMPROVE-IT

- IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (the addition of ezetimibe to statin therapy):
  - **Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?**
  - **"Is (Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)**
  - **Safety of ezetimibe**

Cannon CP AHJ 2008;156:826-32;

Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Patient Population

- Inclusion Criteria:
  - **Hospitalization for STEMI, NSTEMI/UA < 10 days**
  - **Age ≥ 50 years, and ≥ 1 high-risk feature:**
    - **New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD**
  - **LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)**

- Major Exclusion Criteria:
  - **CABG for treatment of qualifying ACS**
  - **Current statin Rx more potent than simva 40mg**
  - **Creat Cl < 30mL/min, active liver disease**

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Dale Doneen METHOD

Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

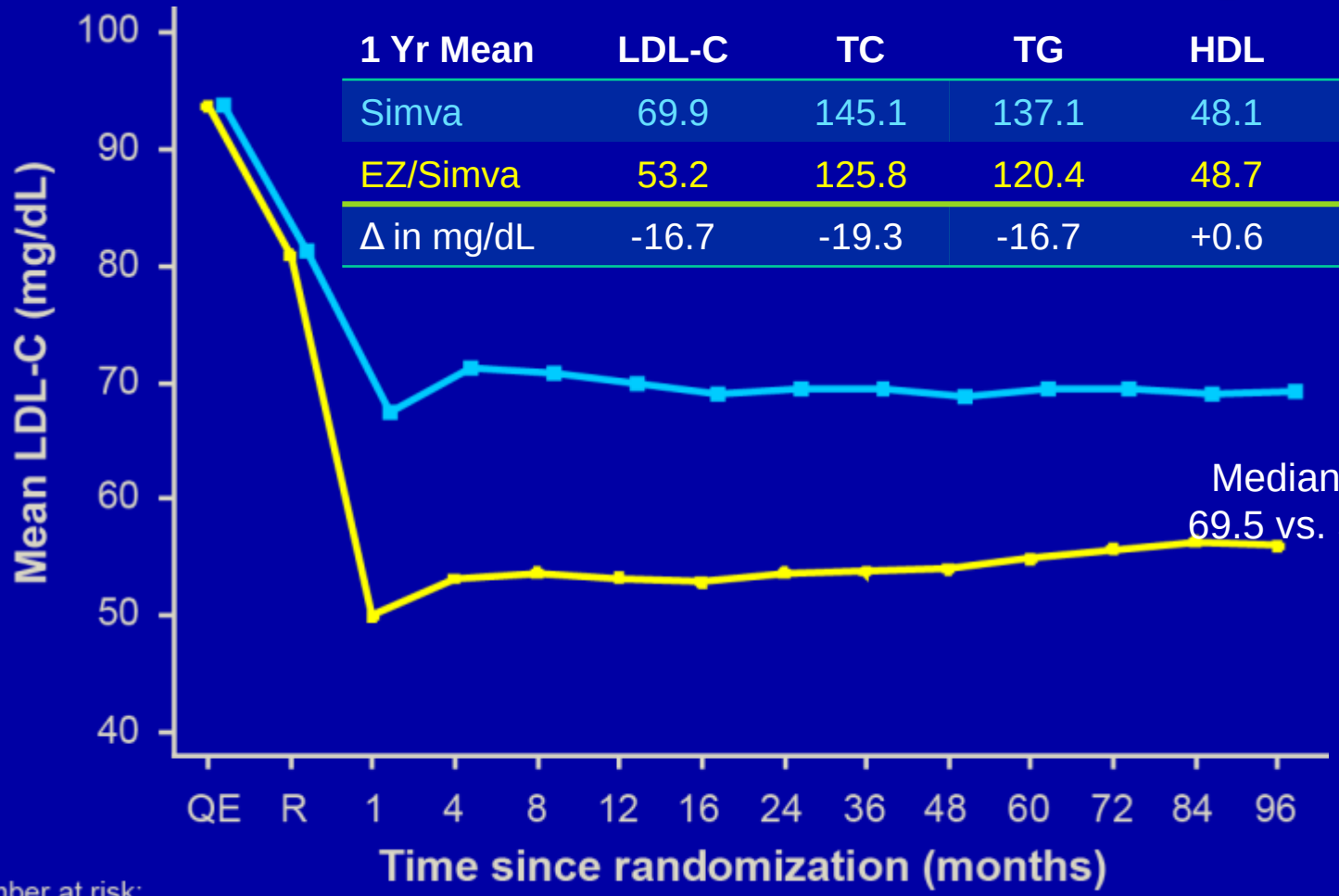
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

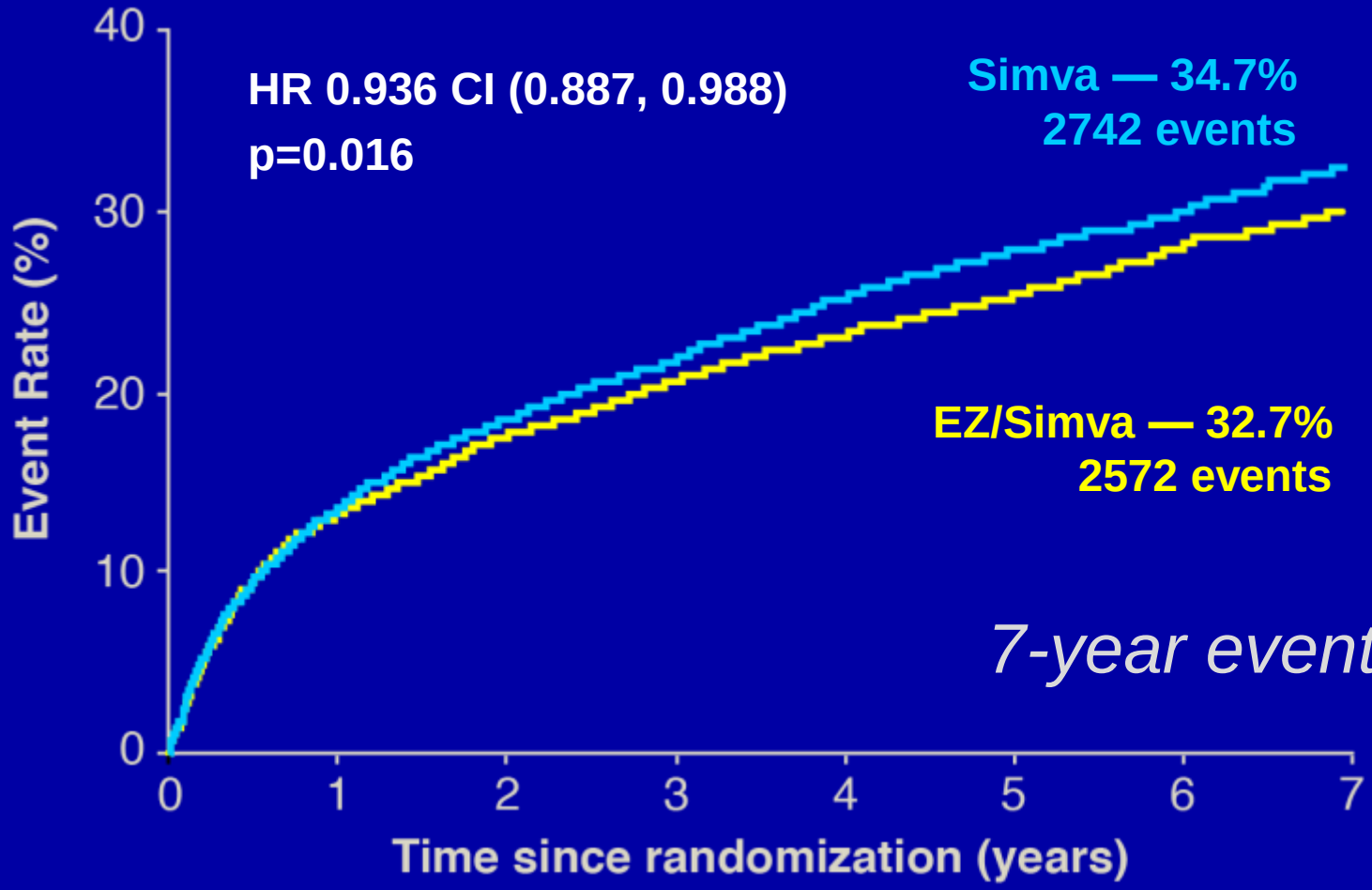
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Dale Doneen METHOD

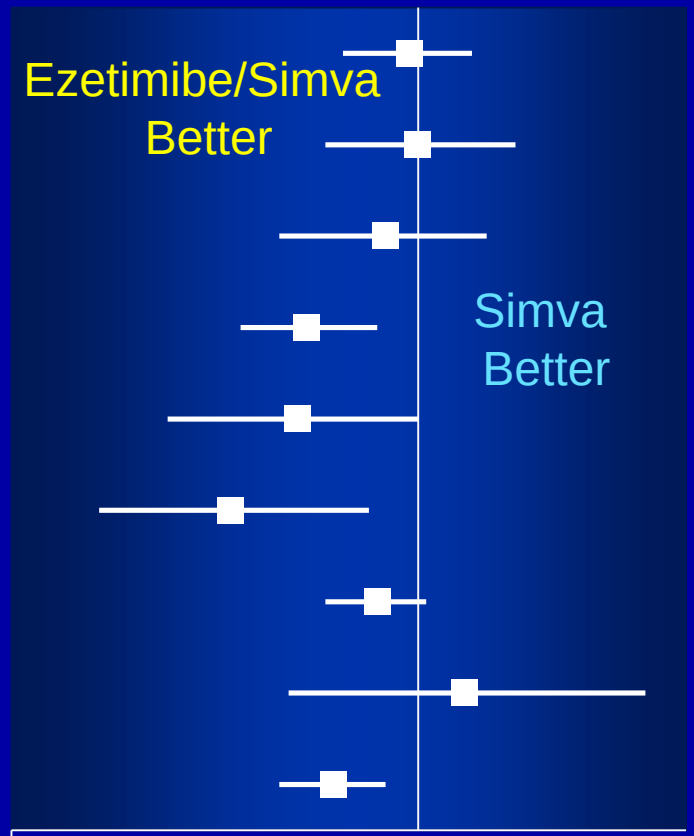
Primary Endpoint

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014; 168:205-12

Individual Cardiovascular Endpoints and CVD/MI/Stroke

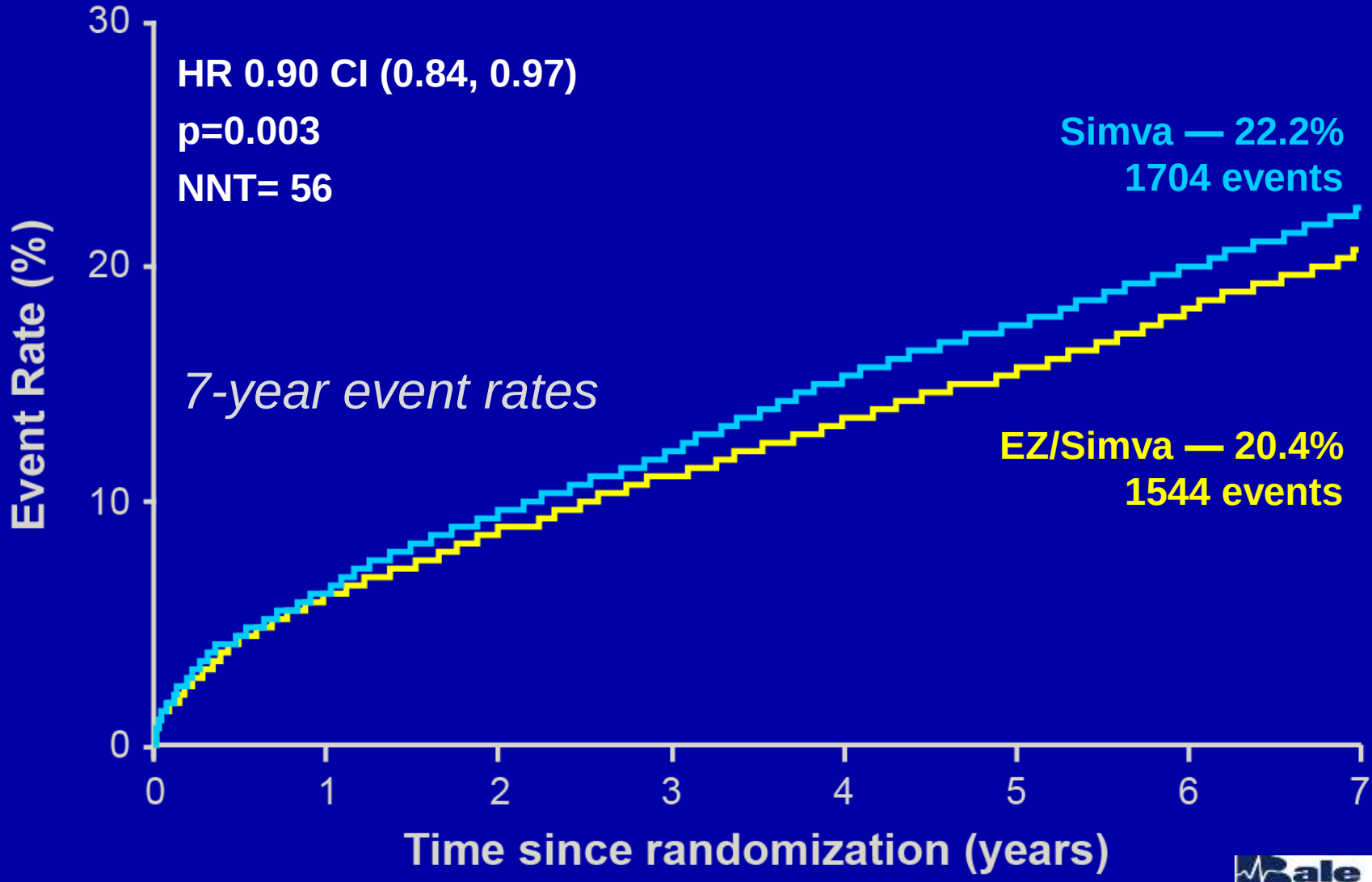


	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

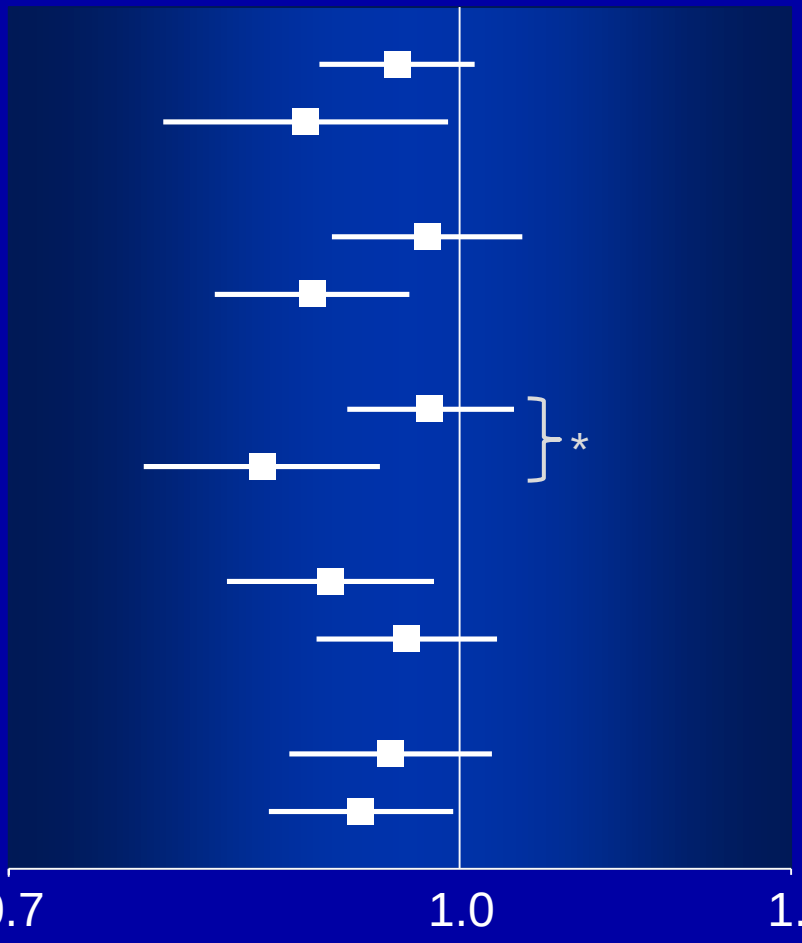
Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

CV Death, Non-fatal MI, or Non-fatal Stroke



Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205

Major Pre-specified Subgroups



	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Safety

- No statistically significant differences in cancer or muscle- or gallbladder-related events

	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee* *% = n/N for the trial duration*

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Conclusions from the IMPROVE-IT Study group

- IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:
  - **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
  - **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
  - **YES:** Confirms ezetimibe safety profile

- Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

- Results could be considered for future guidelines

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

IMPROVE-IT

Bale/Doneen Take-Away

1. Adding ezetimibe to statin therapy is a safe option when further LDL reduction is necessary.
2. Despite lowering LDL levels to <70 (53 mg/dL), there was still a significant 32.7% event rate over 7 years in this high risk population.
3. Vascular disease goes BEYOND an isolated LDL issue
4. Lipid control is an essential element of therapy and ezetimibe may have a role to obtain added LDL control but a significant 67% residual risk of an event remains despite LDL treatment to 53 mg/dL.
5. Pending results of ALL lipids, TC/HDL?, remnant cholesterol, inflammation?

LDL reduction and Cancer Risk

Cancer incidence and mortality in patients on Simvastatin and Exetimibe in Aortic Stenosis (SEAS)

SEAS trial – 1,873 patients found an increased risk of cancer with ezetimibe/simvastatin 10/40 mg/day, relative to placebo.

Registry-based follow-up study over 21 months from the conclusion of the SEAS trial, new incident cancer and total mortality were investigated.

.Green, A., Ramey, D., Emneus, M., et al. Incidence of cancer and mortality in patients from the simvastatin and ezetimibe in Aortic Stenosis (SEAS) Trial. Am. J. Cardiol 2014; 114:1518-1522

Cancer incidence and mortality in patients on Simvastatin and Exetimibe in Aortic Stenosis (SEAS)

Cox proportional analysis of time until death of any cause during follow-up, by follow-up total cohort and follow-up primary cohort

Variable	Hazard Ratio (With 95% Confidence Interval)	
	Follow-Up Total Cohort*	Follow-Up Primary Cohort
Active drug† vs placebo	1.29 (0.82 ; 2.03), p = 0.274	1.23 (0.70 ; 2.15), p = 0.468
Gender: female vs male	1.08 (0.68 ; 1.74), p = 0.741	1.36 (0.77 ; 2.40), p = 0.295
Age >67 years vs ≤67 years	2.42 (1.41 ; 4.17), p = 0.001	1.97 (1.07 ; 3.62), p = 0.029
Smoking: Current vs Other	1.32 (0.98 ; 1.80), p = 0.071	1.17 (0.81 ; 1.69), p = 0.396
Cancer before start of follow-up: Yes vs No	3.57 (2.21 ; 5.79), p <0.001	Not applicable

* Primary statistical approach for death endpoint.

† Ezetimibe/simvastatin 10/40 mg/day.

.Green, A., Ramey, D., Emneus, M., et al. Incidence of cancer and mortality in patients from the simvastatin and ezetimibe in Aortic Stenosis (SEAS) Trial. Am. J. Cardiol 2014; 114:1518-1522

Cancer incidence and mortality in patients on Simvastatin and Exetimibe in Aortic Stenosis (SEAS)

SEAS follow-up had 12 patients with new cancers in the ezetimibe/simvastatin group and 22 in the placebo group (HR 0.55, 95% CI, 0.27 to 1.11) – no difference

SEAS follow-up 43 patients in ezetimibe/simvastatin died and 33 placebo died (HR 1.29, 95% CI, 0.82 to 2.03).

Treatment with Ezetimibe/Simvastatin was not associated with an increased risk for cancer or mortality in the 21 month period after completion of the original SEAS trial.

.Green, A., Ramey, D., Emneus, M., et al. Incidence of cancer and mortality in patients from the simvastatin and ezetimibe in Aortic Stenosis (SEAS) Trial. Am. J. Cardiol 2014; 114:1518-1522

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., Joseph M. Massaro, Ph.D., for the DAPT Study Investigators

N Engl J Med Volume 371(23):2155-2166; December 4, 2014

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

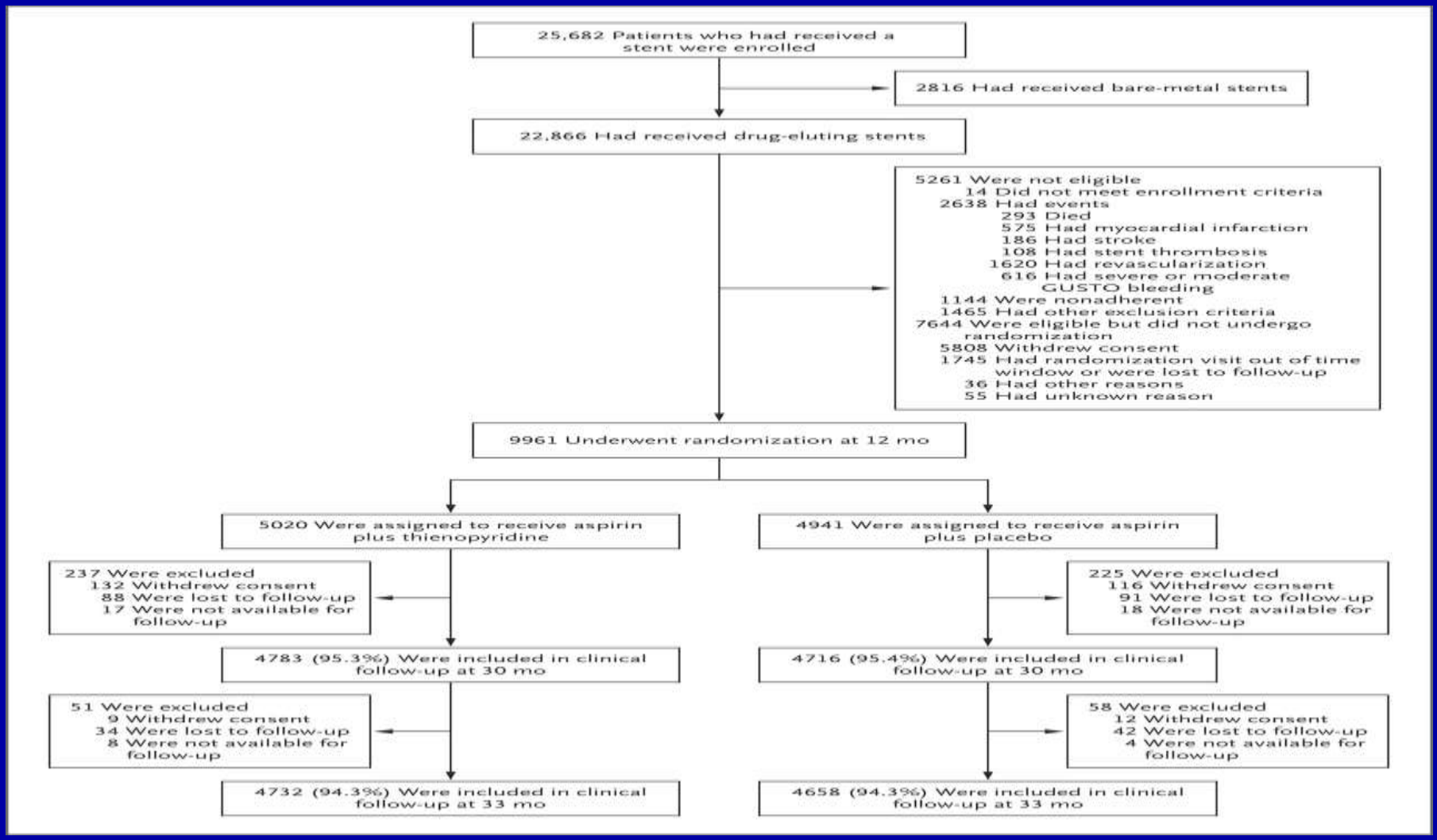
Study Overview

- Patients who had received a drug-eluting stent and then dual antiplatelet therapy for 12 months were randomly assigned to 18 more months of therapy or aspirin alone.

- Continued therapy resulted in lower rates of stent thrombosis and major adverse cardiovascular events but more bleeding.

N Engl J Med Volume 371(23):2155-2166; December 4, 2014

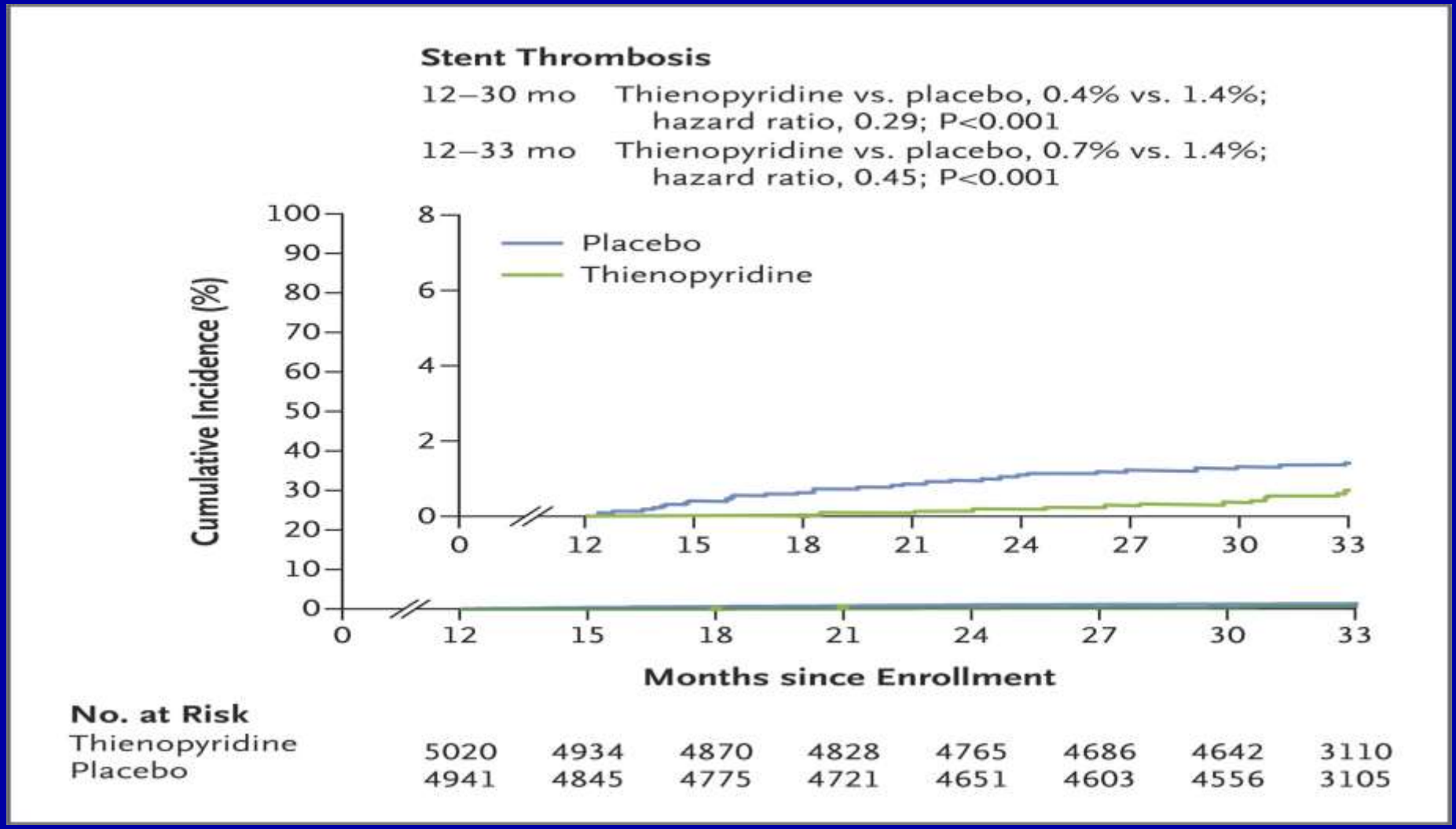
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents



Mauri L et al. N Engl J Med 2014;371:2155-2166

Bale Doneen METHOD

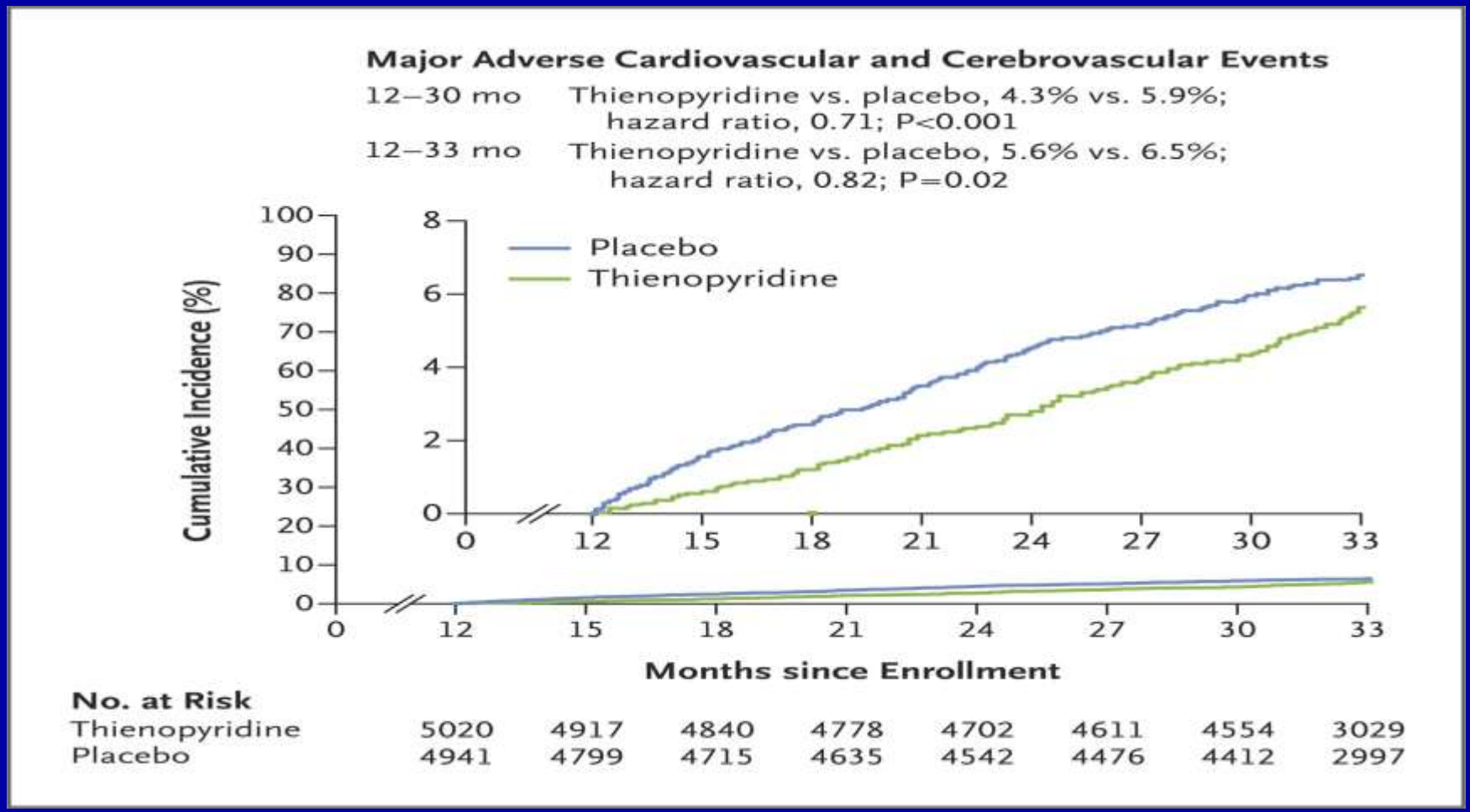
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents



Cumulative Incidence of Stent Thrombosis, According to Study Group.

Mauri L et al. N Engl J Med 2014;371:2155-2166

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents



Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events, According to Study Group.

Mauri L et al. N Engl J Med 2014;371:2155-2166

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N = 5020)	Placebo (N = 4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

* At 12 months after placement of a drug-eluting stent, patients were randomly assigned to receive either continued thienopyridine therapy plus aspirin or placebo plus aspirin for 18 months. Data are presented for the intention-to-treat population. The primary analysis was performed on data from the period of 12 to 30 months after enrollment, and the study coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events. Percentages are Kaplan–Meier estimates.

† The hazard ratios and P values were stratified according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. P values were calculated with the use of a log-rank test.

‡ Definite and probable stent thrombosis were determined according to the criteria of the Academic Research Consortium.

§ The end point of major adverse cardiovascular and cerebrovascular events was a composite of death, myocardial infarction, or stroke.

Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events

Mauri L et al. N Engl J Med 2014;371:2155-2166

Bale Doneen METHOD

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

* The primary safety end point was moderate or severe bleeding as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria. The one-sided test of noninferiority (based on a noninferiority margin of 0.8%) was calculated according to the Farrington–Manning approach. Only patients who could be evaluated were included in this analysis (i.e., patients whose last contact date was ≥510 days after randomization or who had any adjudicated bleeding event at or before 540 days). Patients could have had more than one bleeding episode. The secondary analysis of bleeding, as assessed according to the criteria of the Bleeding Academic Research Consortium (BARC), is shown according to subtype in Table S5 in the Supplementary Appendix.

† One-sided P=0.70 for noninferiority.

Bleeding End Point during Month 12 to Month 30.

Mauri L et al. N Engl J Med 2014;371:2155-2166

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

Mauri L et al. N Engl J Med 2014;371:2155-2166

2015 PRECEPTORSHIP SCHEDULE

February 20-21, 2015

Las Vegas

Renaissance Las Vegas Hotel
3400 Paradise Road

May 29-30, 2015

Atlanta

JW Marriott
Buckhead 3300 Lenox Rd. N.E.

November 6-7, 2015

New Orleans

Renaissance New Orleans Pere Marquettte
817 Commons St.