Bale/Doneen Live Chat Session

June 16, 2011

4-5 pm PST

Amy L. Doneen MSN, ARNP

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Intension of the live chats

- Provide new data
- Discuss “hot” topics
- Review questions proposed by preceptors
- Analyze case studies from audience
- Review upcoming meetings
- Open discussion for remaining

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New Data March-April-May 2011

- ACT NOW
- KIF 6
- Calcium
- NSAIDS
- Atorvastatin and diabetes
- ARBS and MI risk

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Pioglitazone Slashes Risk of Diabetes Conversion 72%

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

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

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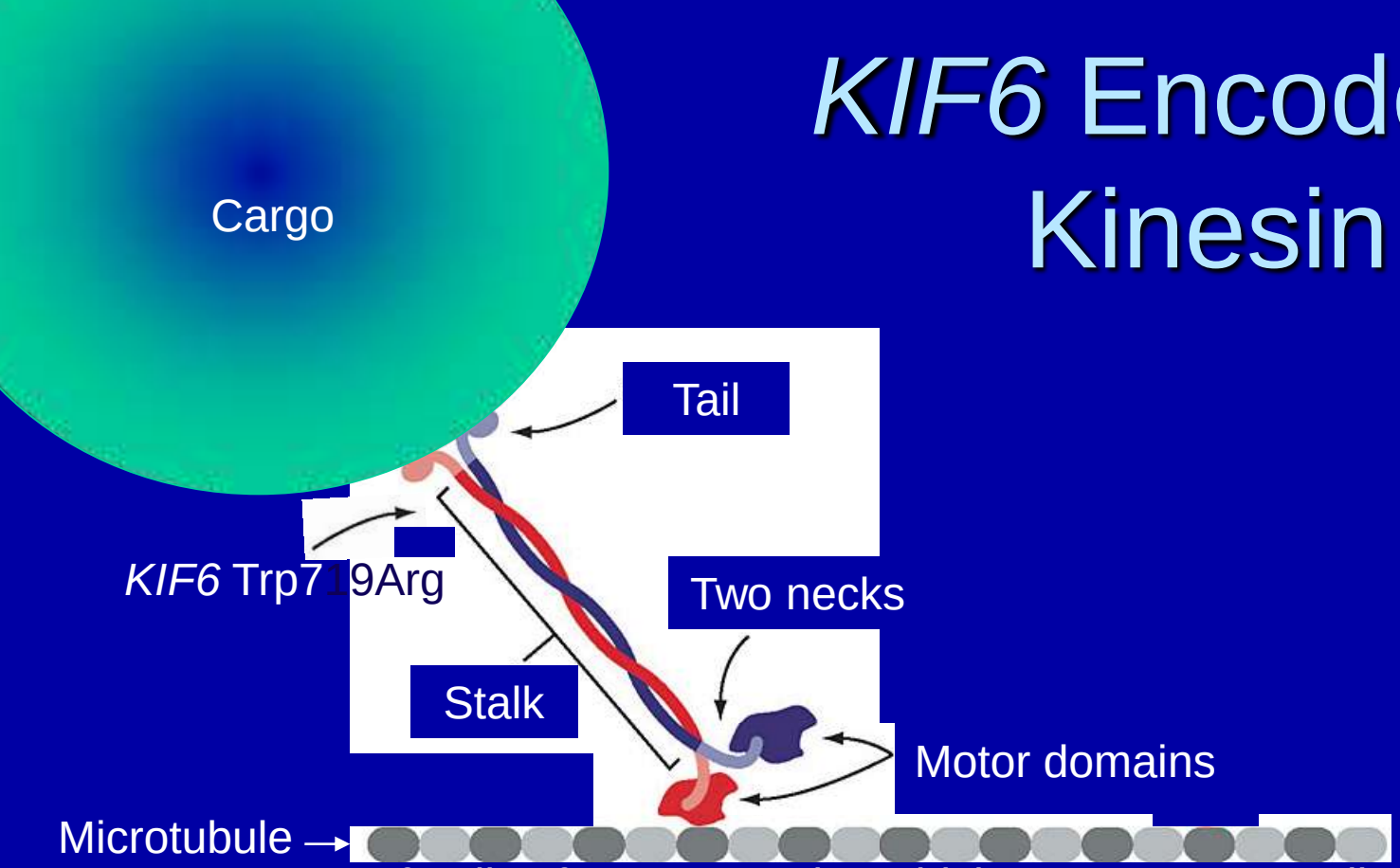
KIF6 Encodes a Kinesin



- Kinesins: a family of motor proteins which transport organelles, protein complexes and mRNAs within a cell
- The genetic variant changes tryptophan to an arginine
- This change results in a non-polar residue replacing a basic residue in the tail domain which may affect cargo binding or regulation in the motor domain

Asbury *et al*. *Science* **302**: 2130 (2003)

Asbury *et al*. *Science* **302**: 2130 (2003)

Does Carrier Status Predict CV Risk ???

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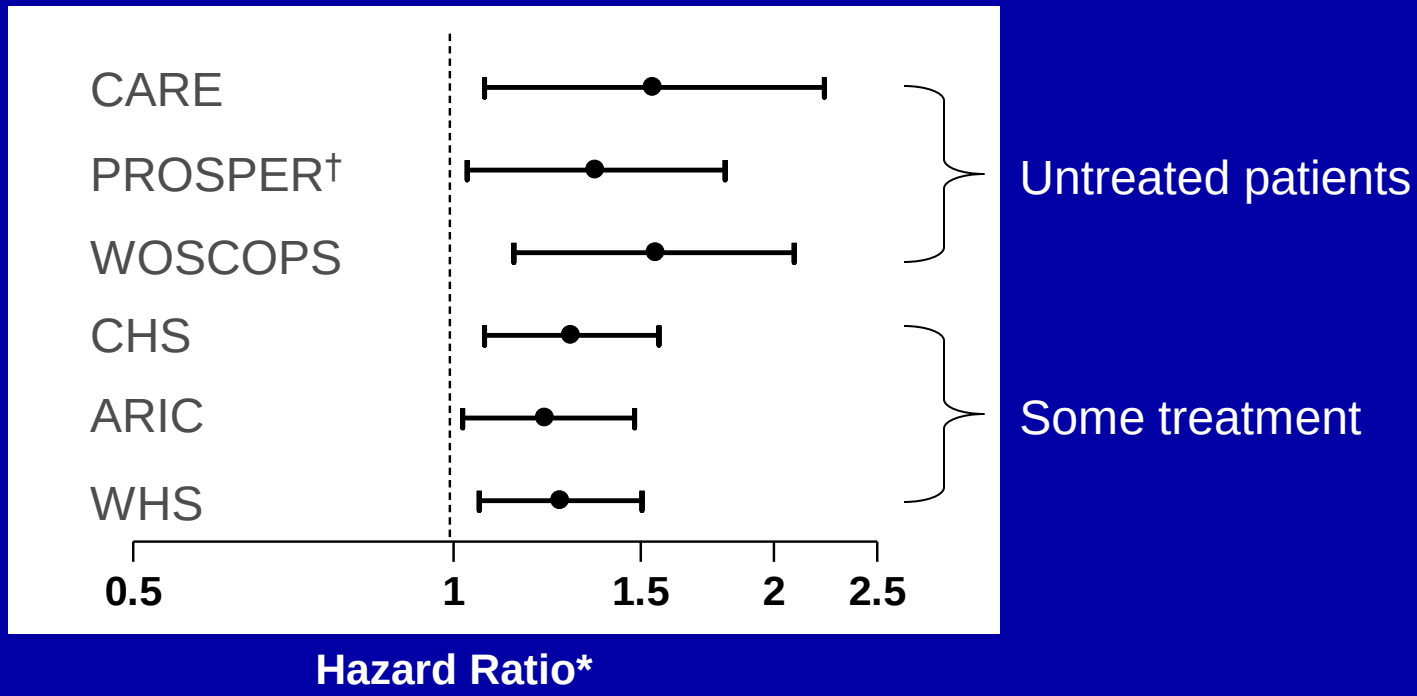
KIF6 Variant is Associated with CHD

Increased Risk in Untreated Populations



- *KIF6* variant predicts risk of CHD
- Up to 55% increased risk in untreated populations

**Adjusted for traditional risk factors*

†PROSPER patients with prior vascular disease

KIF6 not Predictive in Heart Protection Study (HPS)

- 9,181 placebo-treated pts evaluated for risk of vascular events; followed five yrs.

- No significant effect in risk with KIF6

Hopewell JC, et. al. *J Am Coll Cardiol* 2011; DOI:10.1016/j.jacc.2011.02.015. Available at: http://content.onlinejacc.org

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KIF6 did not Predict Risk in Jupiter

- 17,802 low risk pts.; placebo vs. rosuva. 20mg

- No significant difference seen in carriers vs. non-carriers in placebo group

Abstract presentation 2011 ACC meeting

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Does Carrier Status Predict Statin Response??

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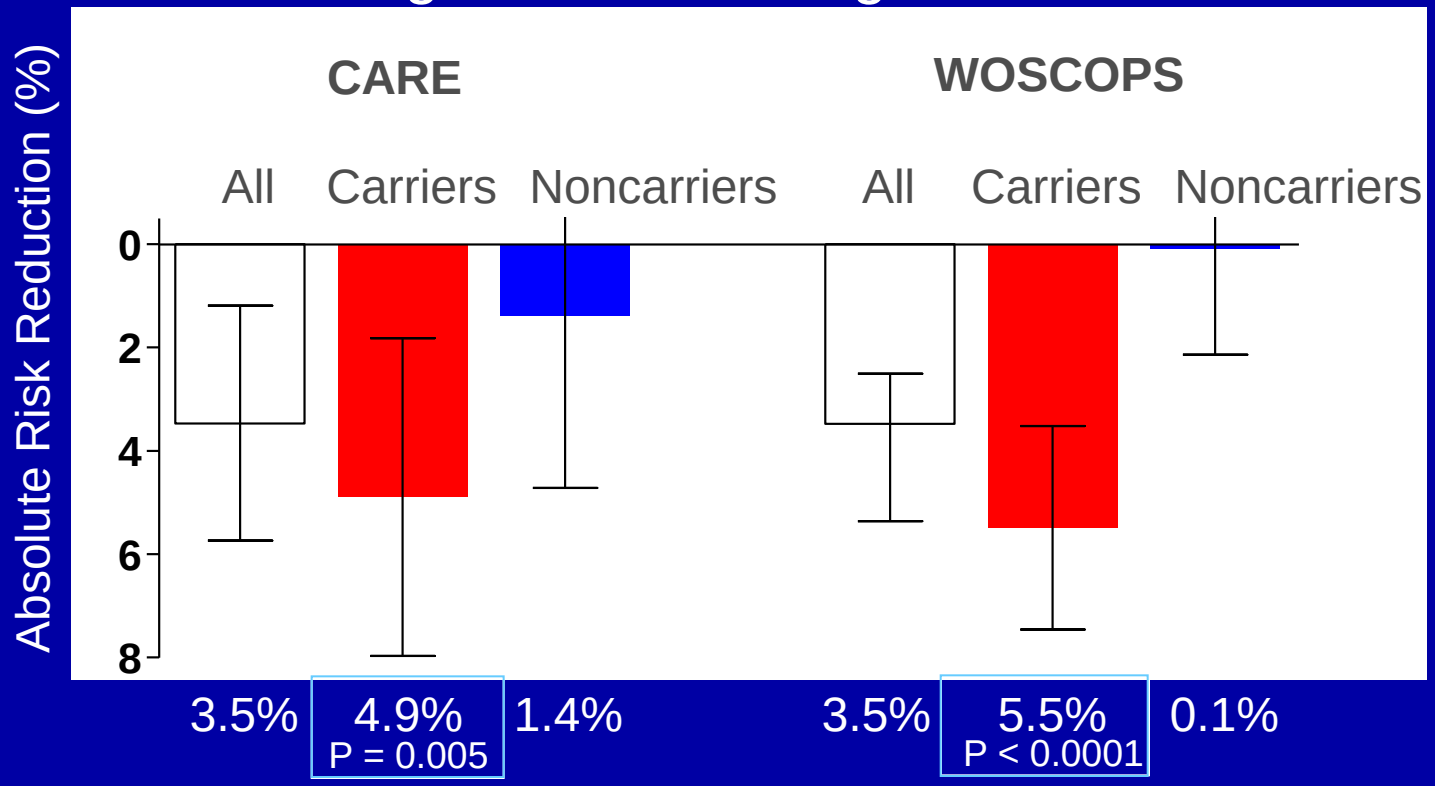
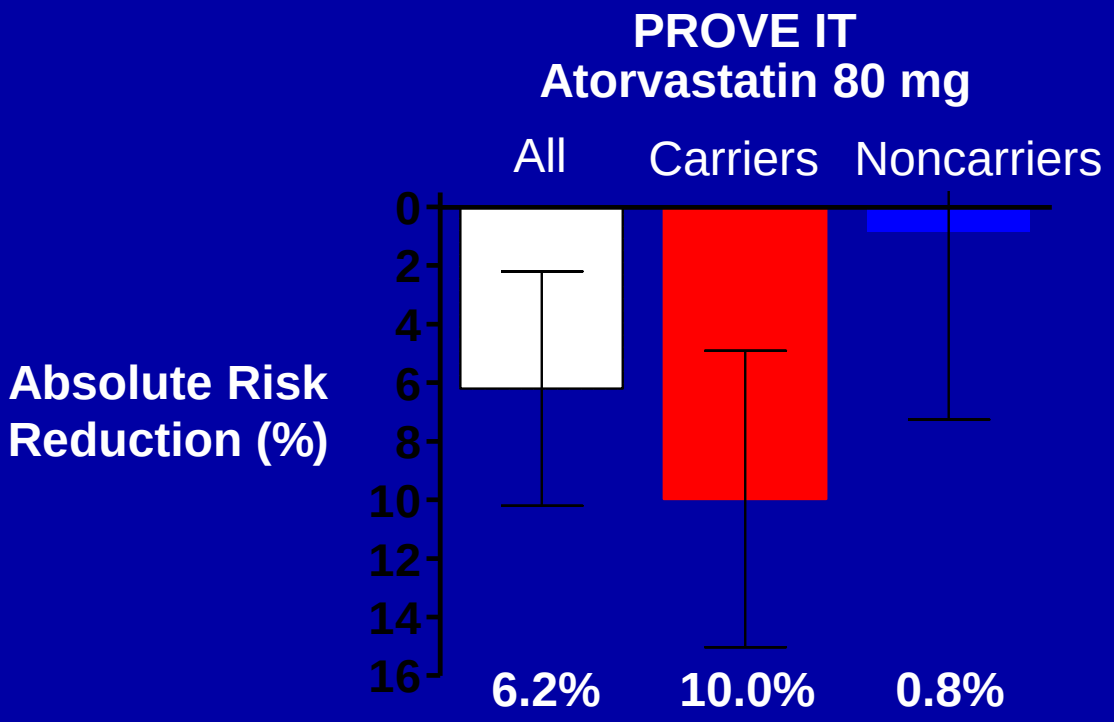
CHD Event Reduction During Pravastatin Tx

According to KIF6 719Arg Carrier Status



- In both CARE and WOSCOPS, carriers of the 719Arg risk allele received substantial and significant reduction of absolute risk for CHD events from pravastatin therapy. No significant reduction was observed in noncarriers
- In WOSCOPS, risk reduction was significantly (P = 0.011) greater in carriers than in noncarriers

Prevention of CHD Events



- Carriers of the *KIF6* risk allele also received significant risk reduction from high dose atorvastatin in PROVE IT, suggesting that the *KIF6* prediction of event reduction may apply to treatment with other statins
- Carriers also received significantly greater benefit than noncarriers (P=0.018)

KIF6 did Predict Statin Response in TNT

- 10,000 stable CHD pts.; atorvastatin 10mg vs. atorvastatin 80mg

- Significant difference seen in homozygous carriers vs. heterozygous carriers or non-carriers

Abstract presentation 2011 ACC meeting

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KIF6 did not Predict Statin Response in Heart Protection Study (HPS)

- 18,343 rx'ed with placebo or simva 40mg

- RR of vascular event with simva:

  23% carriers vs 24% non-carriers - NS

Hopewell JC, et. al. *J Am Coll Cardiol* 2011; DOI:10.1016/j.jacc.2011.02.015. Available at: http://content.onlinejacc.org

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KIF6 did not Predict Statin Response in Jupiter

- 17,802 low risk pts.; placebo vs. rosuva. 20mg

- No significant difference seen in carriers vs. non-carriers with rosuva rx

Abstract presentation 2011 ACC meeting

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KIF6 did not Predict Statin Response in Ideal

- 8,888 stable CHD pts.; simvastatin 20mg vs. atorvastatin 80mg

- No significant difference seen in carriers vs. non-carriers

Abstract presentation 2011 ACC meeting

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Clinical Significance of *KIF6* Testing

KIF6 carriers- may have higher life time CV risk

1. Maintain a disease treatment platform. (EDFROG)
2. Disease = absolute risk
3. Monitor for “cats in the gutter”? Routine evaluation

KIF6 noncarriers

1. Still can be at risk: monitor for disease
2. If using pravastatin or atorvastatin, consider rx beyond mono-statin therapy
3. May want to favor statin therapy with simvastatin or rosuvastatin

Calcium Supplements (even with Vitamin D) show increase CV risk

- Total 30,000 women from placebo controlled trials, most recently the WHI added data set of 17,000:

- Randomized to new supplement use (calcium with Vitamin D) was associated with a statistically significant increase in risk of "clinical MI" (hazard ratio 1.22; p=0.05) and clinical MI and stroke (hazard ratio 1.16; p=0.05)

- 1000 people taking calcium with or without vitamin D would cause six additional MIs or strokes (a number needed to harm of 178) yet prevent only three fractures (a number needed to treat of 302)

- *Borland MJ, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the WHI. BMJ 4.19.2011*

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NSAIDS and CV Risk

31 trials and 116,429 pts on NSAIDS

NSAID	MI	Stroke	Cardiovascular death
Naproxen	0.82 (0.37-1.67)	1.76 (0.91- 3.33)	0.98 (0.41-2.37)
Ibuprofen	1.61 (0.50-5.77)	3.36 (1.00-11.60)	2.39 (0.69-8.64)
Diclofenac (Volyaren)	0.82 (0.29-2.20)	2.86 (1.09-8.36)	3.98 (1.48-12.70)
Celecoxib	1.35 (0.71-2.72)	1.12 (0.60-2.06)	2.07 (0.98-4.55)
Rofecoxib (Vioxx)	2.12 (1.26-3.56)	1.07 (0.60-1.82)	1.58 (0.88-2.84)

Statistically significant

Trelle S, Reichenbach S, Wandel S, et al. *BMJ* 1/2011; DOI:10.1136/bmj.c7086.

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Atorvastatin 80mg versus Placebo Increased Risk of New Onset Diabetes

Trial	Atorvastatin 80 mg	Control	HR (95% CI)	P
SPARCL	8.71	6.06	1.37 (1.08-1.75)	0.011

4731 patients with hx of stroke or TIA but no known CHD

Waters, D., et. al. JACC 4/5/2011

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Higher Doses of Atorvastatin versus Lower Dose of Atorva or Simva Associated with a Trend of Increased Risk of New Onset Diabetes

Trial	Atorvastatin 80 mg	Atorva 10mg-TNT Simva 20mg - Ideal	HR (95% CI)	P
TNT Stable CAD	9.24	8.11	1.10 (0.94-1.29)	0.226
IDEAL Recent ACS	6.40	5.59	1.19 (0.98-1.43)	0.072

Waters, D., et. al. JACC 4/5/2011

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FDA- Olmesartan Benefits Outweigh Potential CV Harm

- 10-month long **FDA** safety review
- Is not recommended as rx to delay or prevent microalbuminuria in diabetic pts
- FDA will perform additional studies and analyses of completed studies, to obtain more information about the CV risks or benefits
- The FDA will update the public when new information is available

Food and Drug Administration. FDA Drug Safety Communication:
Safety Review Update of Benicar (olmesartan) and cardiovascular events. April 14, 2011.

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ARBs do not Reduce Risk of Heart Attack

- Review of 37 randomized trials; 150,000 pts; placebo or active rx; follow-up at least 1 yr; published up to 8/1/2010

- RR of MI 0.99 (95% CI 0.92-1.07)

- RR of HF 0.87 (95% CI 0.81-0.93)

- RR of new-onset diabetes 0.85 (95% CI 0.78-0.93)

- RR of stroke 0.90 (95% CI 0.84-0.98)

Bangalore S, et. al. *BMJ* 4/26/2011; DOI:10.1136/bmj.d2234. Available at: http://www.bmj.com.

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“Hot” Topics

- AIM HIGH
- Actos and Bladder Cancer

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May 26, 2011: AIM HIGH

NHLBI announced that the AIM-HIGH study has been stopped. All AIM-HIGH participants were treated with simvastatin, with the possible addition of ezetimibe, to achieve an LDL-C between 40 and 80 mg/dL. Patients were randomly assigned to also receive either Niaspan or placebo.

The AIM-HIGH data and safety monitoring board recommended stopping the trial as of May 25, 2011 because of lack of efficacy. The data from the interim analysis indicated that the trial does not show a significant difference in cardiovascular outcome event rates between the two study arms. There were 249 primary outcome events (15%) in the simvastatin arm and 262 (15%) in the Niaspan plus simvastatin (p=0.561).

There were a total of 28 ischemic strokes (1.6%) in the Niaspan plus simvastatin arm and a total of 12 such events (0.7%) reported in the simvastatin arm.

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Bale/Doneen Method Thoughts:

This AIM-HIGH announcement and trial cessation allows the opportunity to propose several relevant and important questions.

We must recognize that AIM-HIGH was slated to validate many of our observations of previous clinical trials and certain clinical observations. The NHLBI's decision to halt this trial is based on a lack of efficacy, not an increase risk for clinical events.

Regardless, we await the full disclosure with much anticipation. In the meantime, we are left to search for potential meaning of these preliminary findings, knowing that the full release will hopefully provide the needed information to formulate a clinical decision for our patients.

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Intent to treat

Intent to treat: AIM HIGH was designed as an "intent to treat" study, which allows for individuals to be included in the treatment arm without daily compliance monitoring of medication adherence.

Nine of the ischemic stroke events reported in the Niaspan arm occurred after the subjects had stopped taking Niaspan for 67-1467 days.

Niaspan administration requires careful monitoring to insure compliance with treatment therapy. As we know, if the medication is not taken daily, its treatment benefit is negated.

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Confounding Therapies:

Confounding therapies: Ezetimibe was used in 515 participants as an add-on therapy to the statin therapy with the intent to get LDL to the treated goal of 40-80. It remains yet unclear how many participants in the Niacin/statin ischemic stroke arm were also taking ezetimibe.

The potential interaction between Niaspan and ezetimibe has never been formally evaluated. We do know from the ENHANCE trial and ARBITER 6, that ezetimibe is an effective add-on to statin therapy to lower LDL. It has been determined, however, that the addition of ezetimibe to a statin falls short of improving atherosclerosis, as measured by carotid intima-media thickness. We also do not know the potential relationship of ezetimibe and Niaspan – this remains unclear.

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Population:

Population: Inclusion criteria for the study subjects included established cardiovascular disease and atherogenic dyslipidemia.

This demographic possesses a multi-factorial treatment challenge, often including obesity, hypertension, insulin resistance and metabolic syndrome. This study was designed to treat the lipid portion of this risk factor profile.

In this difficult to treat population, therapy beyond the lipids is essential. Treatment issues include blood pressure management, psychosocial management, exercise support, diet support, sleep management and optimal treatment of insulin resistance.

Clearly, this trial perhaps supports the opportunity to recognize the multi-factorial treatment necessary to treat stroke risk in this complicated patient population.

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AIM HIGH: CVA, MI, Inflammation…

Stroke Prevention: The INTERSTROKE trial provides the best insight into the most common causes of ischemic stroke. The most common cause of ischemic stroke, worldwide, was determined to be blood pressure. We do not know how well BP was controlled in these patients. TC/HDL target – AIM HIGH low enough?

***Heart Attack Prevention*:** The INTERHEART trial looked at a worldwide population and it was determined that lipids were the number one risk factor for heart attacks. AIM-HIGH is a lipid trial and, according to the preliminary release, heart attack concerns were not raised by the NHLBI safety board. Also – TC/HDL target – AIM HIGH low enough?

***Arterial Inflammation*:** Events are triggered by inflammation. Eradication of arterial inflammation in individuals who are resistant to insulin frequently requires therapy beyond statin and niacin. It will be interesting to see the trial results in regards to biomarkers of inflammation.

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Bale/Doneen AIM HIGH thoughts

The story is yet to unfold and we will be watching the daily press releases with the intent to determine the true reason for this rather surprising announcement. We share the same concerns as many providers who are dedicated to the prevention of heart attacks, ischemic stroke and diabetes. The story will continue….

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6.11.2011
Actos and Bladder Cancer

The French drug regulatory authority (AFSSAPS) has called a halt to all formal marketing of pioglitazone (Actos) and is recommending that physicians should not prescribe any more drugs containing pioglitazone.

They have made these statements based on a signal that pioglitazone may be associated with a small increase in bladder cancer in diabetics, suggesting that the risk of bladder cancer may outweigh the intended glycemic control of the drug in diabetic subjects.

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Current analysis

- Takeda, is conducting a ten-year, observational cohort study as well as a nested case-control study in patients with diabetes who are members of Kaiser Permanente Northern California (KPNC) health plan. Patients selected in this study had diabetes mellitus and were ≥40 years of age at study entry. Patients with bladder cancer prior to study entry or within six months of joining KPNC were excluded from this study. The cohort included 193,099 patients with diabetes.

- A planned five-year interim analysis was performed with data collected from January 1, 1997 through April 30, 2008. The median duration of therapy among Actos-treated patients was 2 years (range 0.2-8.5 years). The study investigators did not observe a statistically significant association between any Actos exposure and increased bladder cancer risk in the study (Hazard ratio = 1.2, 95% CI: 0.9-1.5).

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Bladder Cancer Information

- Bladder cancer is estimated to occur in 20 per 100,000 persons per year in the United States and is thought to be higher in diabetics. This equals 1/5000 http://www.cancer.gov/statistics.

- An estimated 70,530 new cases of bladder cancer cases were diagnosed in 2010. It is more common in men than women. The most common type of bladder cancer is Urothelial carcinoma, comprising 90-95% of all bladder cancers and is strongly associated with cigarette smoking.

- The recent pioglitazone data does not highlight what kind of bladder cancer was increased in the diabetic patient.

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Risk vs Benfit of Pioglitazone

- The PROACTIVE data demonstrates that 11.3% of 2605 diabetics on Actos had a CV death, MI, stroke or ACS= 294, 13.9% of 2603 diabetics not on Actos had a CV death, MI, stroke or ACS = 361.
- Therefore, 66 fewer events in 2.8 years or 23 fewer events per year per approx. 5,000 diabetics occurred in the Actos arm.
- Comparing with bladder cancer, it is accepted that about one diabetic out of 5,000 per year will get bladder cancer regardless of glycemic treatment.
- Appreciating Actos' benefit of MI and CVD prevention, it would have to increase the risk of bladder cancer about 20 fold to offset the intended cardiovascular benefit.

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Diabetes Prevention….

- In terms of preventing diabetes, Actos has published, randomized, prospective data showing a 72% reduced risk of developing diabetes (ACT NOW).

- We have good evidence that if a patient becomes diabetic by age 50, he or she will lose about 25-30% of their lifespan. It is known that becoming diabetic at any age will impact the quality and quantity of life.

- Therefore, the prognosis of bladder cancer becomes extremely pertinent. Again our conjecture is that the official agency rendering judgment on Actos is only considering its benefit as one of sugar control, as this is its only formal indication. We are in a different position because our use of Actos also includes the prevention of CV events and diabetes. Therefore, we must weigh the risk to benefit ratio on that basis.

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Actos and Bladder Cancer

- The best prevention of bladder cancer is to avoid smoking. People who smoke are at a three to four fold higher risk of getting this disease.

- Because of the recent concern with Actos and bladder cancer, we feel it necessary to continue to educate our patients on the risks of smoking and its link to cancer.

- We will specifically consider the safety of pioglitazone in our smoking patients and perhaps perform routine urine tests for the presence of hidden hematuria, as the most common symptom of bladder cancer is blood in the urine. We also embrace this as an opportunity to educate our patients on the intended benefit and risk of their cardiovascular prevention program.

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Recent Questions…..

- Protocol for Aspirin Resistance –what is it?
- AAA screening with 9P21
- What cases other than coronary artery disease can cause elevated MPO?
- Treatment for elevated MPO

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Aspirin Resistance

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Aspirin resistance linked to worse outcomes

- 20 secondary-prevention studies; 3000 people
- aspirin from 75 mg/day to 325 mg/day; platelet-function assay
- 28% were classified as aspirin resistant
- cardiovascular events occurred in 39% ASA resistant pts.
- cardiovascular events in 16% ASA sensitive pts.
- concomitant clopidogrel and/or a GP IIb/IIIa inhibitor provided no additional benefit in people who were aspirin resistant
- underestimated the benefits of ASA; if only aspirin-sensitive patients are considered, the true level of risk reduction is likely greater than 50%

Krasopoulos G et al. *BMJ* 1/18/2008; available at: http://www.bmj.com.

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Repeat stroke more likely in aspirin non-responders

- 653 patients treated for secondary-stroke prophylaxis
- 129 found to be non-responsive to aspirin
- 57 (66%) of the 87 patients who had recurrent strokes were non-responsive to aspirin
- patients who were responsive, only 5% suffered recurrent stroke
- odds ratio for a recurrent stroke is 14 times greater in non-responders

Gengo FM, Rainka M, Robson M, et al. Prevalence of platelet non-responsiveness to aspirin in patients treated for secondary stroke prophylaxis and in patients with recurrent ischemic events. *J Clin Pharmacol* 3/2008; 48: 335-343.

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Aspirin Significantly Reduced CV Events in Primary Prevention

Meta-analysis of 90,000 individuals

End point	Odds ratio (95% CI)	p
Total CHD	0.85 (0.69-1.06)	0.154
Nonfatal MI	0.81 (0.67-0.99)	0.042
Total CV events	0.86 (0.80-0.93)	0.001
Stroke	0.92 (0.83-1.02)	0.116
CV mortality	0.96 (0.80-1.14)	0.619
All-cause mortality	0.94 (0.88-1.01)	0.115

Bartolucci AA, et. al. *Am J Cardiol* 5/8/2011; DOI:10.1016/j.amjcard.2011.02.325. Available at: http://www.ajconline.org

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Aspirin Resistance protocol

- 81 mg Aspirin for anyone with atherosclerosis
- Stay on consistent dose x 3 weeks and order: www.accumetrics.com – VerifyNow Aspirin (VerifyNow P2Y12)
- If therapeutic (<550 ARU) – ok
- If non-therapeutic – increase to two 81mg and repeat the test in 3 weeks.

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AAA Screening with 9P21

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AAA Screening

- USPSTF guidelines recommend AAA screening for men aged 65 to 75 years with a hx of smoking

- Problem with above 'guideline':
  1) women experience a third of AAA ruptures
  2) women comprise 40% of AAA deaths
  3) non-smokers comprise 22% of AAA deaths

- Currently about 1.1 million AAAs in the US; aged 50 to 84; USPSTF criteria would miss about 70% of AAA!

Kent KC, et al. *J Vasc Surg 8/*2010; DOI: 10.1016/j.jvs.2010.05.090. Available at: **http://www.jvascsurg.org**.

9p21

- 50% of Caucasians and Asians are heterozygotes
  ~ 25% ⇧ risk of MI/CHD, 49% ⇧ risk of young age MI, 36% ⇧ risk of AAA compared non-carriers

- 23% of Caucasians and Asians are homozygotes
  ~ 56% ⇧ risk of MI/CHD, 102% ⇧ risk of young age MI, 74% ⇧ risk of AAA compared to non-carriers

1. Helgadottir, A, et al. Science 316 (5830): 1491-1493.
2. Helgadottir,A, et al. Nature Genetics 40 (2): 217-224.

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Myeloperoxidase

- Initial slides from CHL – Dr. Marc Penn (slides 48-55)

- Treatment ideas

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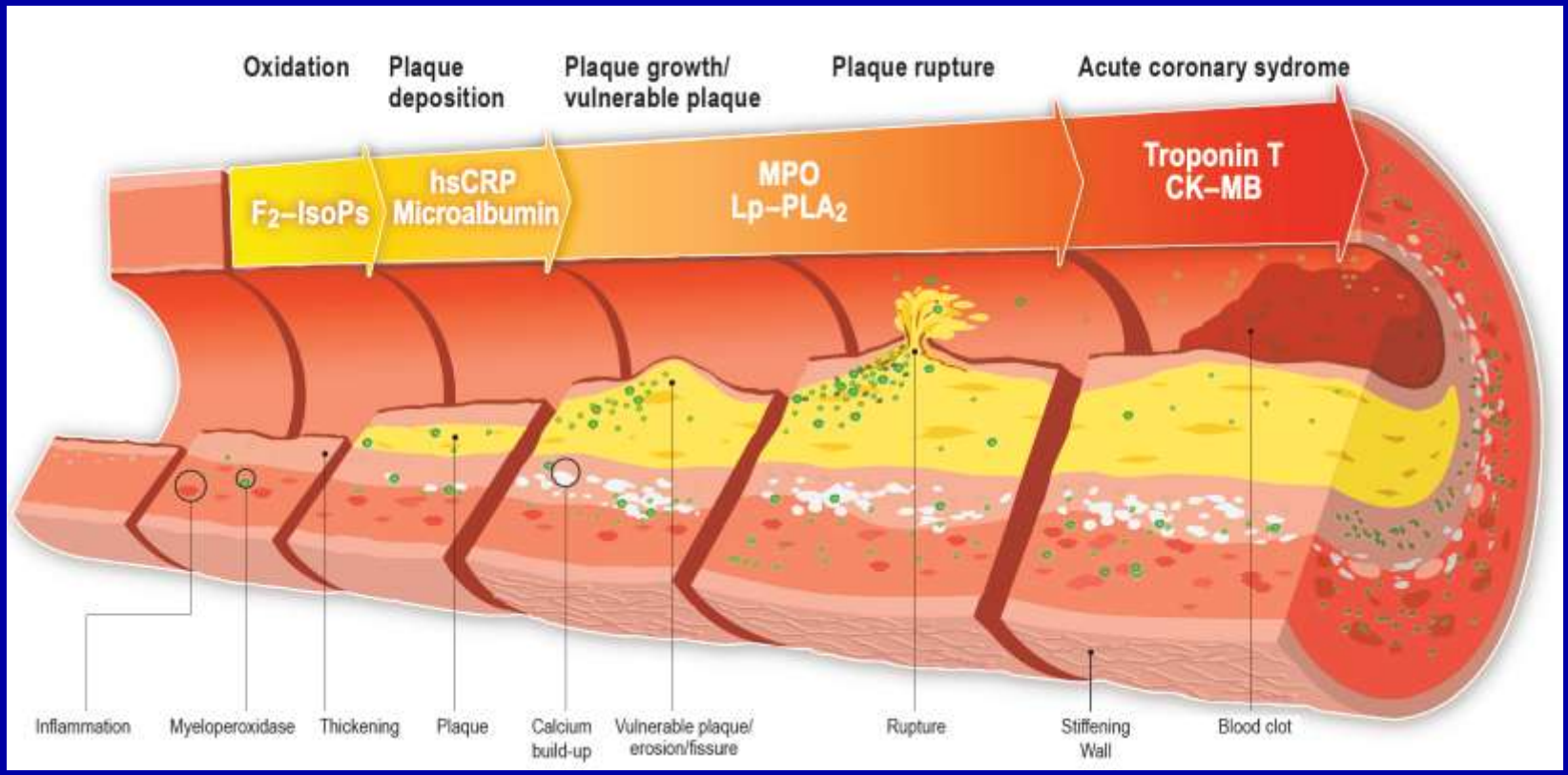
Cleveland HeartLab – Inflammatory profile

Spectrum of Risk



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Bale Doneen METHOD

Introduction to Myeloperoxidase (MPO)

- An enzyme synthesized and stored within polymorphonuclear leukocytes (PMNs) and monocytes
- MPO generates potent anti-microbial oxidants
  - Used by invading PMNs and monocytes to kill bacteria and other pathogens
  - However, oxidation products can damage surrounding vasculature, and are enriched within human atherosclerotic plaque
- MPO is a *specific marker* of plaque vulnerability

Myeloperoxidase (MPO)

What does MPO measure?

- The amount of leukocyte activity in response to arterial inflammation or erosion
- Increased levels of MPO indicate increased risk for plaque rupture

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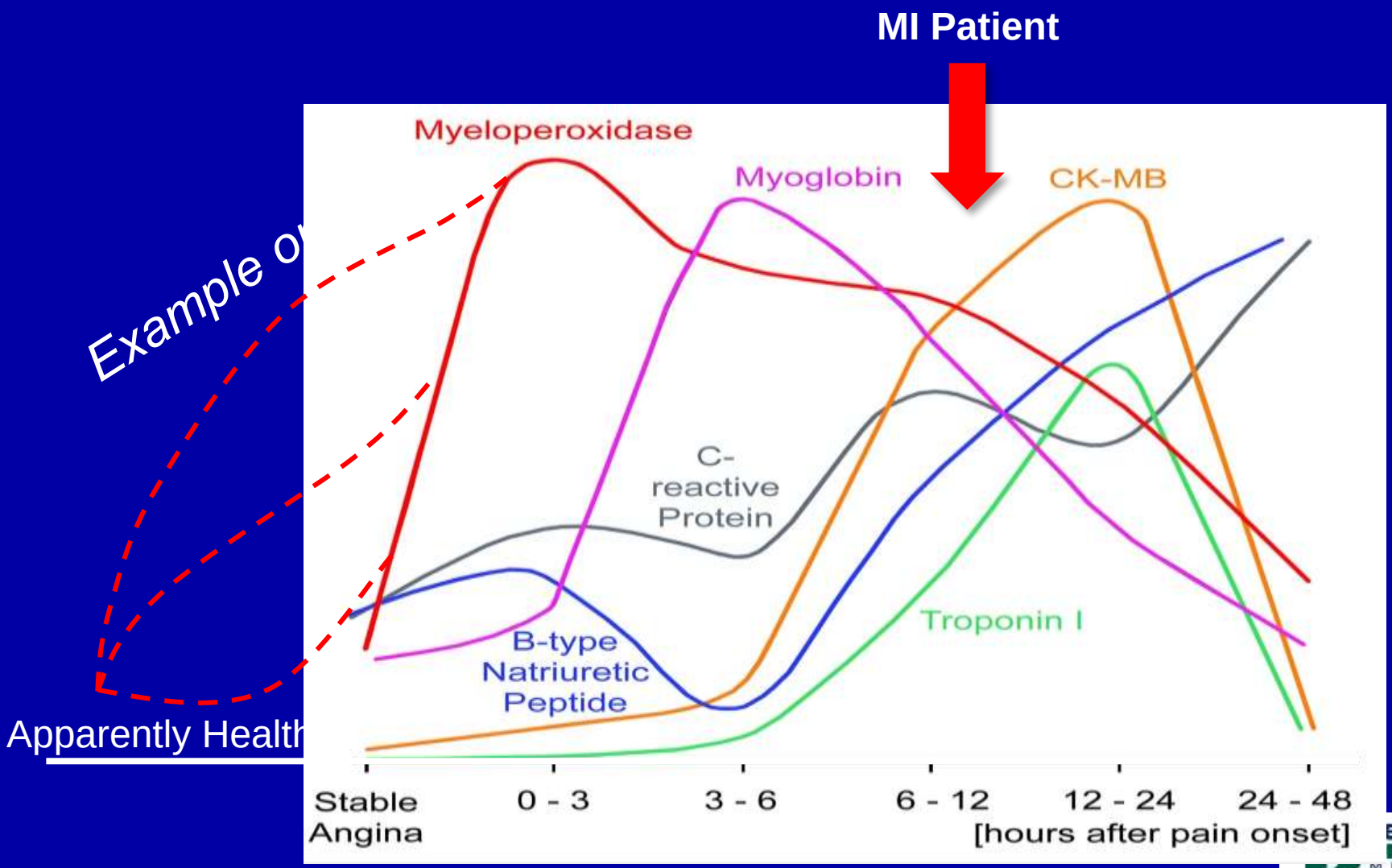
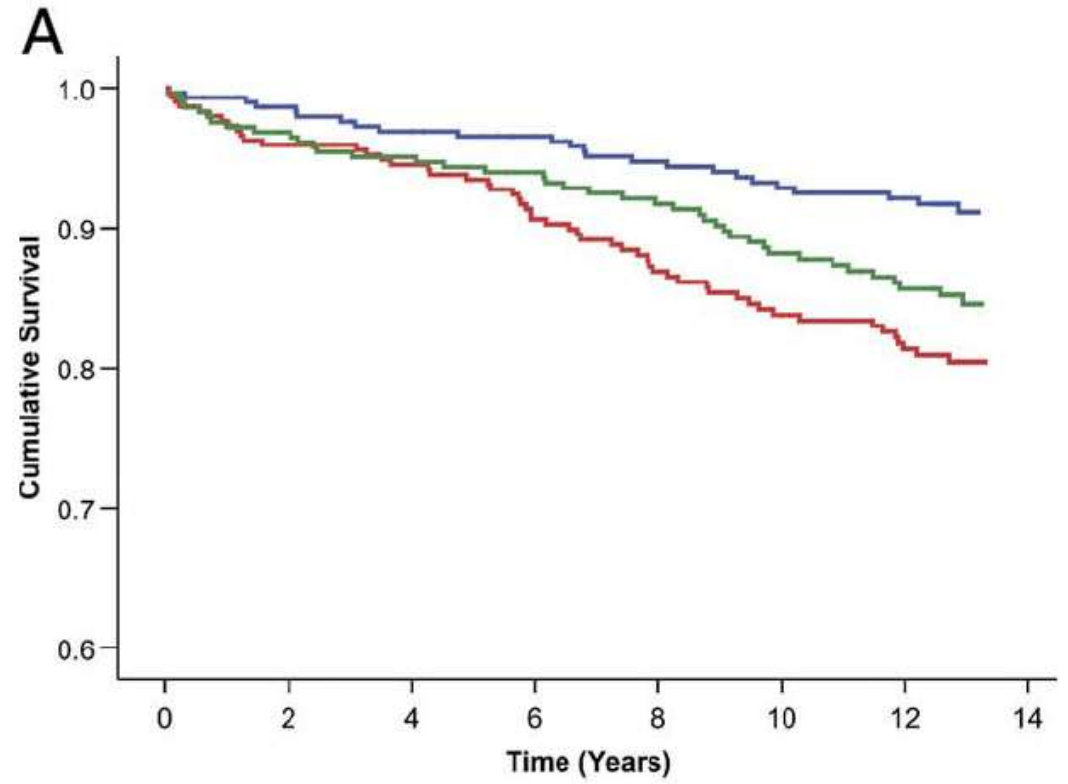
Time release of various inflammatory biomarkers



Clinical implications of MPO testing

- Elevated MPO levels predict cardiovascular mortality at 13 yrs in patients with angiographic evidence of CAD[1]



First tertile (lowest)

Second tertile

Third tertile (highest)

HR: 2.38 (95% CI: 1.47-2.98) for top vs bottom MPO tertile

[1]Modified from Heslop CL et al. Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography. *J Am Coll Cardiol* . 2010; 55 [illegible] 02 110

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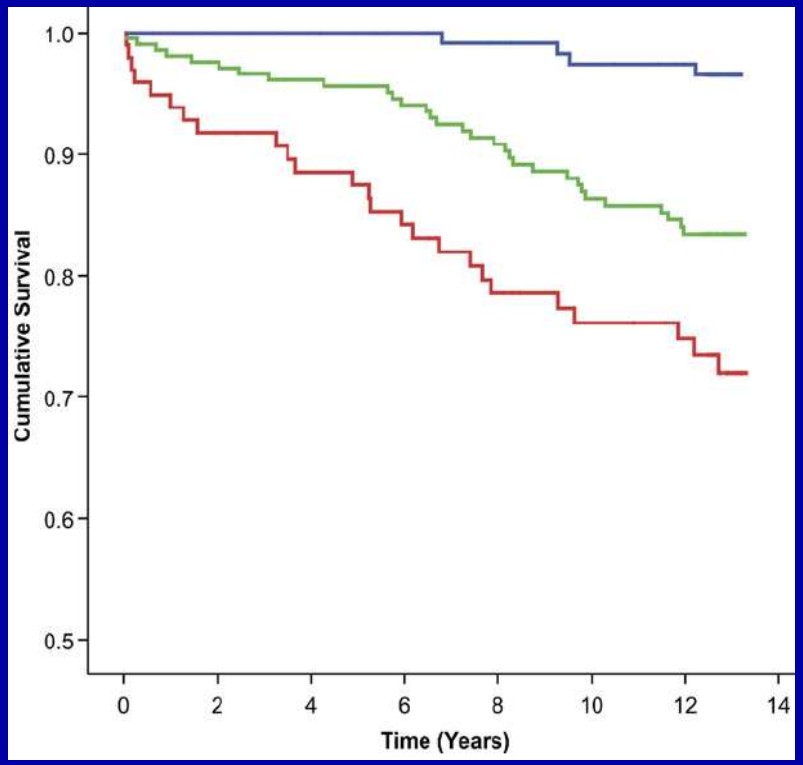
Clinical implications of MPO testing

- MPO and CRP have combined utility in predicting cardiovascular mortality risk in patients with angiographic evidence of CAD[1]



MPO CRP

Low and Low

High or High — Patients with either a high MPO or high CRP elevated had 5.3-fold higher mortality risk

High and High — Patients with high levels of both MPO and CRP had a 4.3-fold risk vs. patients with only one elevated marker

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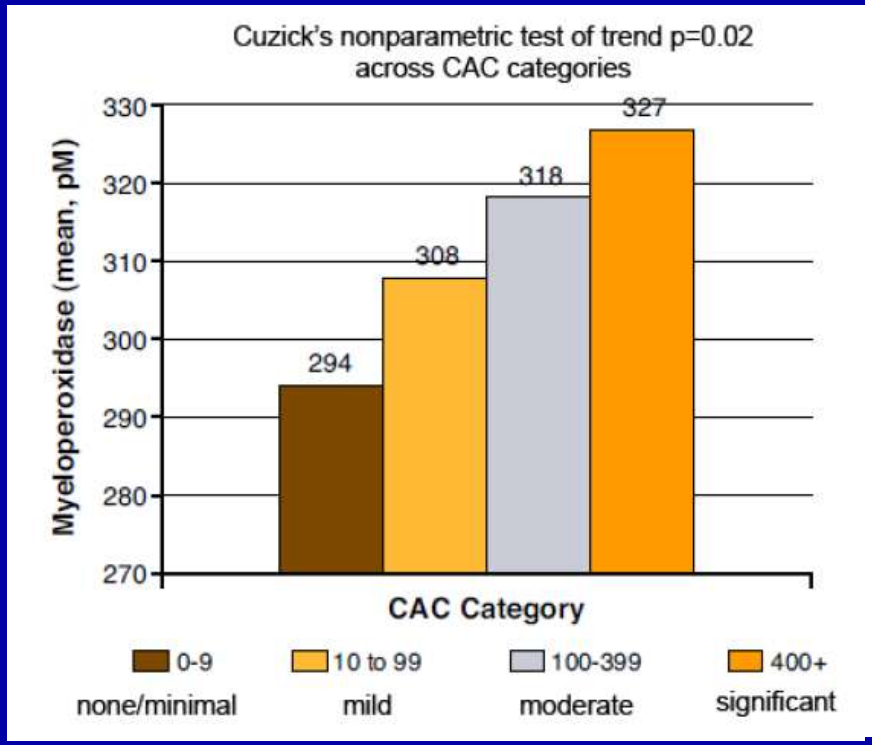
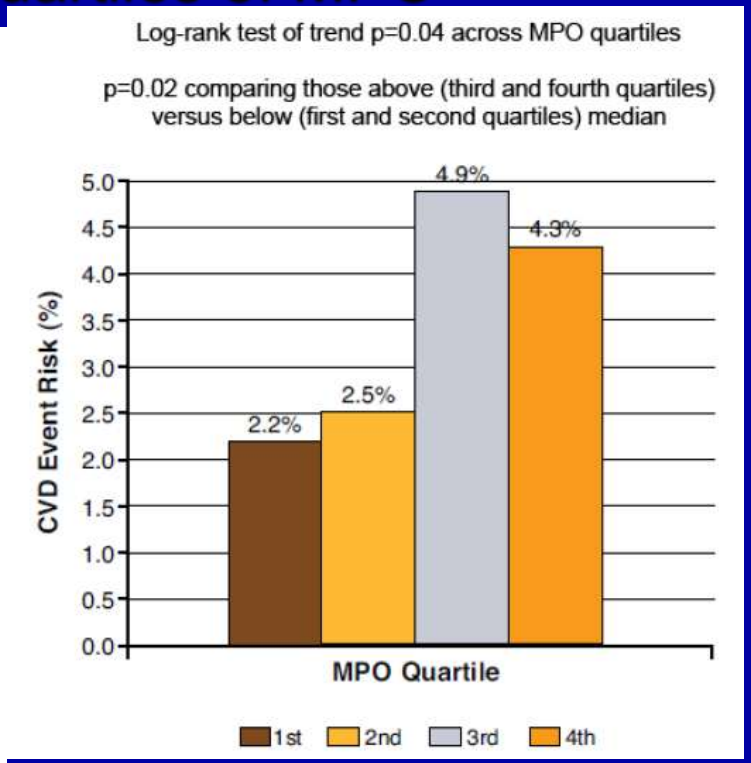
[1]Modified from Heslop CL et al. Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography. *J Am Coll Cardiol* . 2010; 55:1[illegible]-1109

Pale Pioneer METHOD

Clinical implications of MPO testing

- In apparently healthy individuals, mean MPO levels were greater according to increasing CAC categories, and the risk for CVD increased by quartiles of MPO[1]





[1]Wong ND et al. Myeloperoxidase, subclinical atherosclerosis, and cardiovascular disease events. *J Am Coll Cardiol Img.* 2009; 2: 1093-1099.

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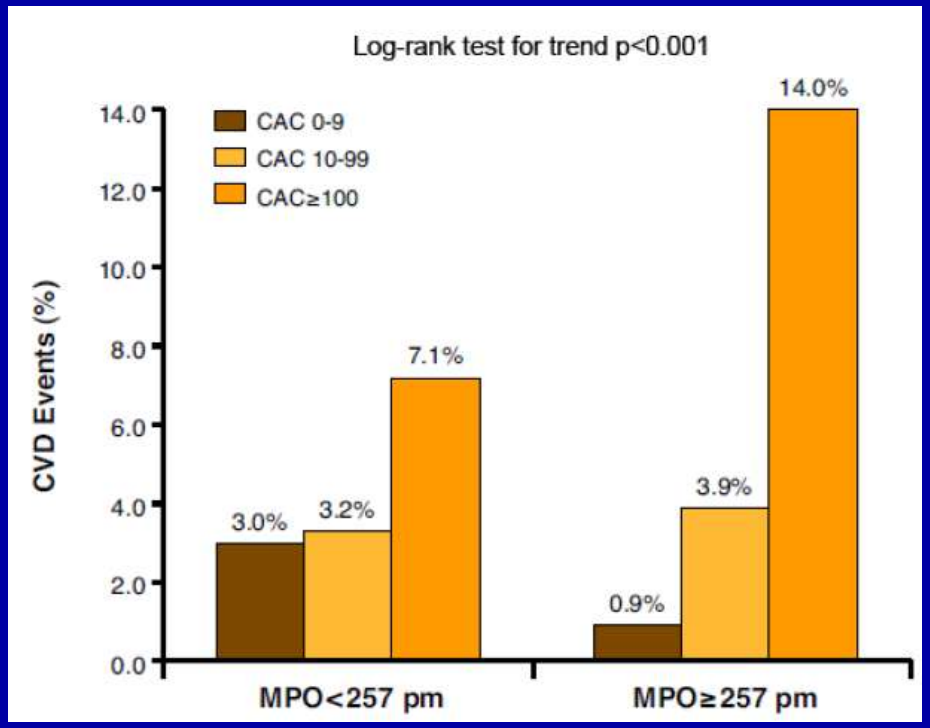
Dale Doneen METHOD

Clinical implications of MPO testing

- In apparently healthy individuals, moderate and significant CAC (≥100) and MPO levels (≥257 pm) demonstrated increased risk for CVD[1]



MPO levels ≥ 257 pm remained an independent predictor of CVD events even after adjusting for various risk factors (HR: 1.9, p=0.04)

[1]Wong ND et al. Myeloperoxidase, subclinical atherosclerosis, and cardiovascular disease events. *J Am Coll Cardiol Img.* 2009; 2: 1093-1099.

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Dale Doneen METHOD

MPO is Detrimental to the Lipids

- HOCl oxidizes apo B-100
- Reactive nitrogen species oxidize LDL (NO_2LDL)
- Oxidizes HDL
- Nitrotyrosine and chlorotyrosine bind to apo A-1 and HDL

  interferes with ABCA-1 reverse cholesterol transport

  chloronated-HDL competes as a ligand for SR-B1

Nicholls, S.J.; Hazen, S.L., ***Arterioscler. Thromb. Vasc. Biol.*** 3/2005;25;1102-1111

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MPO can create vulnerable plaques

- HOCl promotes activation of MMP-7 - promotes fibrous cap rupture

- HOCl promotes endothelial apoptosis and detachment:

  apoptotic endothelial cells are prothrombotic

  superficial erosions can trigger events

Nicholls, S.J.; Hazen, S.L., ***Arterioscler. Thromb. Vasc. Biol.*** 3/2005;25;1102-1111

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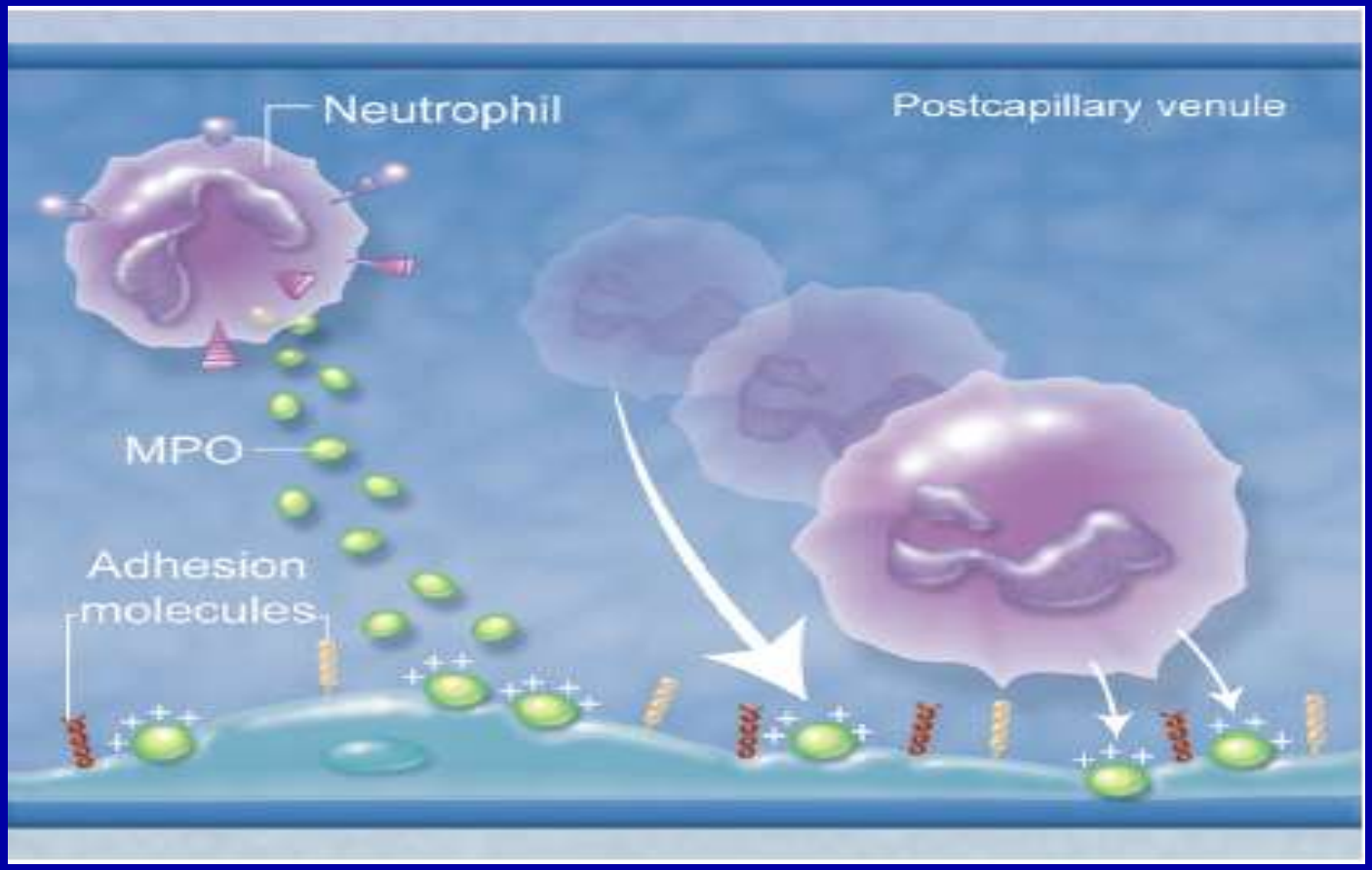
MPO may Attract Neutrophils to the Endothelium Magnetically



MPO may not only be directly injurious, but may also promote adherence of neutrophils to the endothelium leading to additional inflammatory damage

Hickey, M. J. ***Blood*** 2011 117: 1103-1104

Myeloperoxidase (MPO), predicts future risk of coronary artery disease in healthy people

Regardless of other known risk factors !

Meuwese MC et al. *J Am Coll Cardiol* 7/2/2007; available at: http://content.onlinejacc.org.

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Case:

When to use Plavix?

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Case

- 51-year-old male well known to me for some years who recently suffered a mild TIA, followed by a lacunar 2 weeks later in April 2011.
- Patient was intermittently compliant with his hypertensive medications.
- Resistant to taking a statin, he was placed on Zetia 10 mg daily several years prior to this incident
- Once he was discharged from the hospital, got a BHL, CIMT
- Carotid Doppler reveals minimal plaque otherwise no significant stenosis.
- CYP2C19, and aspirin resistant tests are pending.
- CIMT thickness was elevated at 1.098, in addition his plaque burden was 8.718 mm.
- Apo E was 4/4, if KIF 6 positive, 9P 21 heterozygous positive
- Abdominal sonogram revealed that he had a borderline aneurysmal dilatation of the mid abdominal aorta up to 3 cm.

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Case continued

- Question has come up between CV Specialist and Neurologist on whether or not to continue him on Plavix.

- Currently on Simcor 40/1 g daily. In addition he is still taking his Zetia 10 mg daily, diagnosed with OSA, BP in good control with benazepril 40, Chlorthalidone 25 and amlopidine 5 daily. BHL 4MyHeart – losing weight.

- Should he take plavix?

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EDFROG

- 1. Does he understand what caused his stroke?
- 2. He has established vascular disease
- 3. Inflammation – hsCRP, MACR, Fibrin, Lp-PLA2, MPO
- 4. Root Causes - ?
  - Insulin resistance
  - Lipo(a)
  - MPO
  - Vitamin D
  - Periodontal disease
- 5. Optimal Goals – BP, lipids sugars
- 6. Genetics - +KIF 6 and +9P21, CYP2C19?, LPA?, Apo E 4

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Treatment

- Foundation for atherosclerosis
  - Lifestyle – Apo E 4, exercise, laughter, OSA, etc
  - Statin – Simvastatin 40mg
  - RAAS – Benazapril
  - Omega 3 – Apo E 4 – keep at 1 gm/day
  - Antiplatelet
    - Aspirin (resistance pending)
    - Plavix? (9P21 pending)
- Additional:
  - Niaspan 1 gm, Zetia 10, CCB, Diuretic

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Question remaining -

- Root causes – have they all been uncovered and is treatment adequate?
- Inflammation – arterial wall stability?
- Should plavix be included?

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CHARISMA subgroup analysis Primary Prevention efficacy results

End point	ASA+placebo, n=1141 (%)	ASA+clopidogrel, n=1148 (%)	p
MI, stroke, or CV death	4.7	5.7	0.30
CV death	1.8	3.0	0.07

ASA=aspirin

analysis that adjusted for baseline patient characteristics, demographics, medications, and clinical history, use of clopidogrel was on the cusp of significance as a predictor of CV death, with a hazard ratio of 1.72 (95% CI 0.99-2.97; p=0.05).

Wang TH et al. *Eur Heart J* 8/2/2007: available at: http://eurheartj.oxfordjournals.org.

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CHARISMA subgroup analysis in Secondary Prevention efficacy results

End point	Clopidogrel plus aspirin (%)	Aspirin alone (%)	HR (95% CI)	p
CV death/MI/ stroke	7.3	8.8	0.83 (0.72–0.96)	<0.01
Hospitalization for ischemia	11.4	13.2	0.86 (0.76–0.96)	<0.008

9478 patients with documented prior MI, stroke, or symptomatic PAD

Bhatt DL et al. *J Am Coll Cardiol* 5/15/2007; 49:1982-1988.

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AHA statement post CHARISMA

- Patients who are candidates for clopidogrel
  - Post MI
  - Post angioplasty for MI or unstable angina
  - Post stent
  - Post TIA or ischemic stroke
  - PAD
- Patients who are not candidates for clopidogel
  - Patients who have stable CVD on long-term aspirin therapy
  - Primary prevention group even with multiple risk factors

Updated AHA Statement. 3/16/2006. www.americanheart.org

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Clopidogrel plus aspirin may reduce secondary stroke risk

- risk of recurrent stroke following a TIA or minor stroke is high: approximately 8% at seven days, 12% at 30 days, and up to 20% at 90 days
- 396 pts. rx'ed for 90 days; all on ASA 81mg; 35 recurrent strokes
- 3.7% reduction in recurrent stroke among individuals on active clopidogrel, compared with placebo.

The Fast Assessment of Stroke and Transient Ischemic Attack (TIA) to Prevent Early Recurrence (FASTER) trial. 16th European Stroke Conference; June 1, 2007; Glasgow, Scotland. .

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ACTIVE-A: Strokes by treatment group

End point	Clopidogrel, n (%/y)	Placebo, n (%/y)	Relative risk (95% CI)	p
All strokes	297 (2.4)	409 (3.3)	0.72 (0.62–0.84)	<0.0001
Ischemic stroke	236 (1.9)	343 (2.8)	0.68 (0.58–0.80)	<0.0001
Hemorrhagic stroke	30 (0.23)	22 (0.17)	1.37 (0.79–2.37)	0.26

The ACTIVE Investigators. *N Engl J Med* 2009: available at: http://www.nejm.org.

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Thoughts?

- Plavix – yes or no?
- What about CYP 2C19 and Plavix resistance testing – Example……

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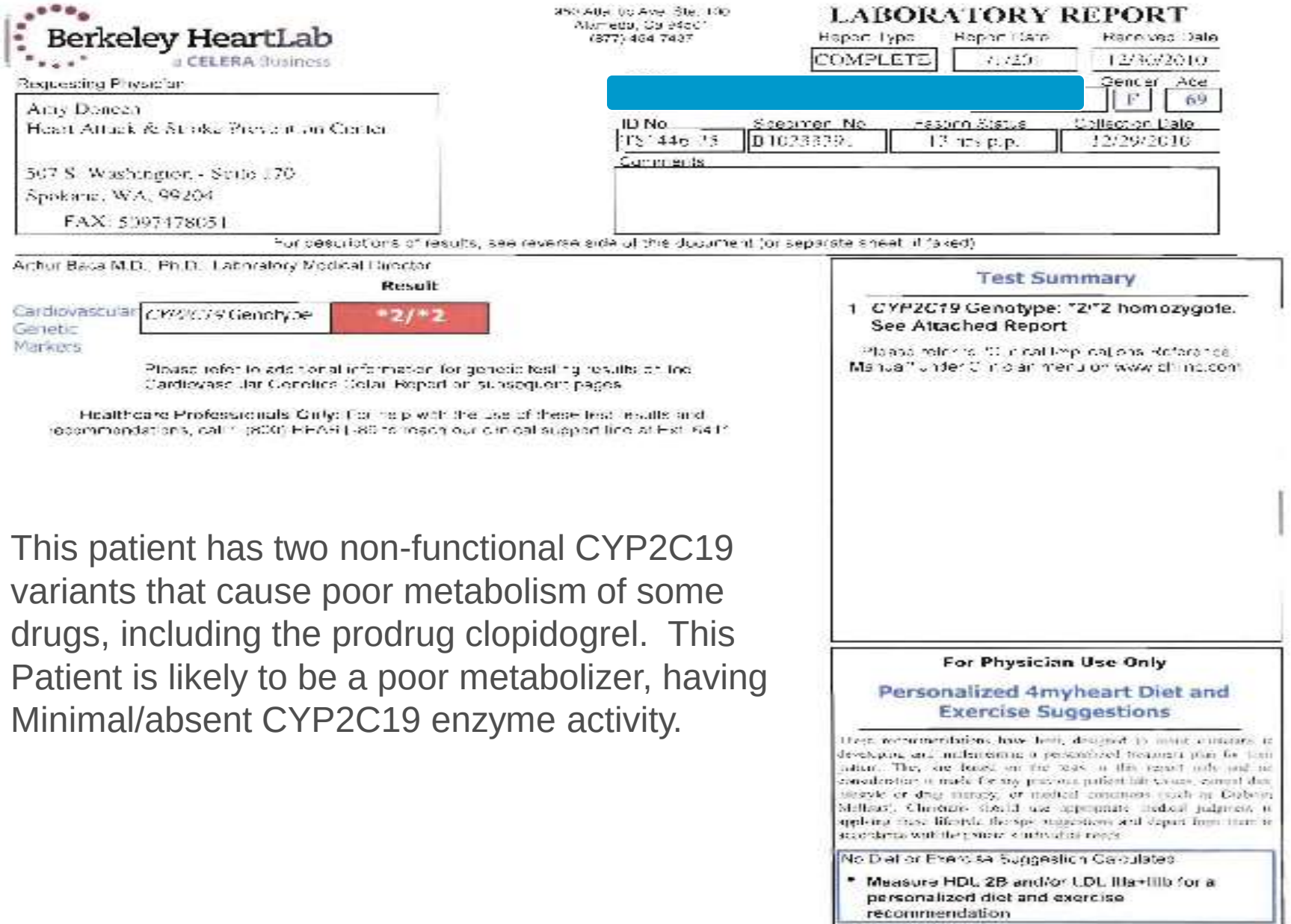
Patient of Amy's – example of CYP 2C19 and resistance testing



Berkeley HeartLab
a CELERA Business

LABORATORY REPORT

Report Type: COMPLETE
Report Date: 1/4/10
Received Date: 12/30/2010

Requesting Physician:
Amy Doneen
Heart Attack & Stroke Prevention Center
507 S. Washington - Suite 120
Spokane, WA, 99204
FAX: 5097478051

Gender: F
Age: 69

ID No: TS 44e 15
Specimen No: B10238839
Specimen Status: 13 tubes p.p.
Collection Date: 12/29/2010

Comments:

For descriptions of results, see reverse side of this document (or separate sheet if faxed)

Arthur Baca M.D., Ph.D., Laboratory Medical Director

	Result	
Cardiovascular Genetic Markers	CYP2C19 Genotype	*2/*2

Please refer to additional information for genetic testing results on the Cardiovascular Genetics Global Report on subsequent pages.

Healthcare Professionals Only: For help with the use of these test results and recommendations, call (800) HEART-88 to reach our clinical support line at Ext. 6417

Test Summary

1 CYP2C19 Genotype: *2/*2 homozygote. See Attached Report

Please refer to Clinical Implications Reference Manual under Clinical Menu on www.clinic.com

For Physician Use Only

Personalized 4myheart Diet and Exercise Suggestions

These recommendations have been designed to assist clinicians in developing and implementing a personalized treatment plan for their patient. They are based on the test results and no consideration is made for any previous patient lab values, current diet, lifestyle or drug therapy, or medical concerns (such as Diabetes Mellitus). Clinicians should use appropriate medical judgment in applying these lifestyle therapy suggestions and depart from them as appropriate with the patient's individual needs.

No Diet or Exercise Suggestion Calculated

- Measure HDL 2B and/or LDL IIa+IIIb for a personalized diet and exercise recommendation

This patient has two non-functional CYP2C19 variants that cause poor metabolism of some drugs, including the prodrug clopidogrel. This Patient is likely to be a poor metabolizer, having Minimal/absent CYP2C19 enzyme activity.

Plavix Resistance Test

- VerifyNow P2Y12 Assay
- Uses ADP as agonist to induce platelet activation and measures impairment of platelet function (degree of platelet P2Y12 receptor blockade)
- Second channel with thrombin receptor agonist to approx. baseline function (do not need to stop the Plavix rx)
- Up to 30% of pts. have inadequate response*

Malinin,A, et. al. ***Thromb Res*** 2007;119(3):277-284
*Serebruany, VL, et. al. ***J Am Coll Cardiology*** 2005: 45:246-251

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VerifyNow P2Y12 Assay

- **Platelet Reactivity P2Y12 – (194-418)** – this indicates the amount of ADP-mediated aggregation specific to the platelet P2Y12 receptor. PRU is determined based on the rate and extent of platelet reactivity (by way of aggregation) in the ADP channel. This provides the extent of platelet aggregation in the presence of clopidogrel.

- **PLT FUNCT BASE - (194-418)** – indicates the amount of thrombin receptor activating peptide (TRAP)-mediated aggregation specific to the platelet PAR-1 and PAR-4 receptors. The BASE result serves as an estimate of baseline platelet function independent of P2Y12 receptor inhibition. The BASE estimates the total possible platelet aggregation regardless of the presence of clopidogrel.

- **P2Y12 INHIBITION - (presurgical <20%)** – this is the percent change from baseline aggregation, and is calculated from the PRU result and the BASE result. Expected values are in the range of 0-100%. Higher percent inhibition values and lower PRU values are reported if the thienopyridine has produced the expected antiplatelet effect.

VerifyNow is a registered trademark of Accumetrics, Inc.

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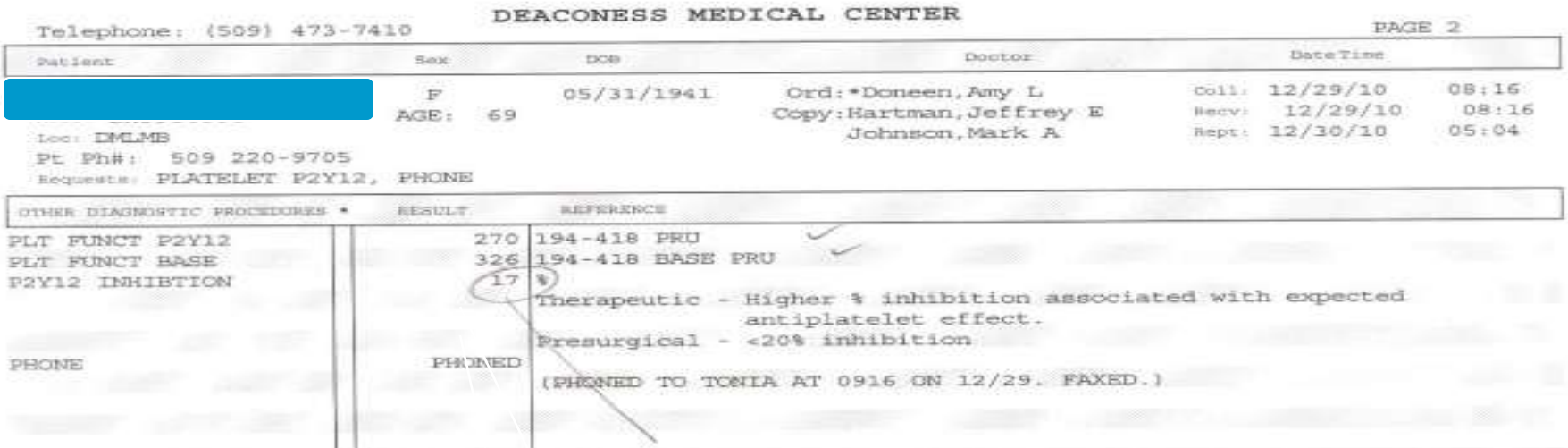

DEACONESS MEDICAL CENTER

Telephone: (509) 473-7410 PAGE 2

Patient	Sex	DOB	Doctor	DateTime
[redacted]	F AGE: 69	05/31/1941	Ord:*Doneen,Amy L Copy:Hartman,Jeffrey E Johnson,Mark A	Coll: 12/29/10 08:16 Recv: 12/29/10 08:16 Rept: 12/30/10 05:04

Loc: DMLMB
Pt Ph#: 509 220-9705
Requests: PLATELET P2Y12, PHONE

OTHER DIAGNOSTIC PROCEDURES *	RESULT	REFERENCE
PLT FUNCT P2Y12	270	194-418 PRU
PLT FUNCT BASE	326	194-418 BASE PRU
P2Y12 INHIBTION	17	%
		Therapeutic - Higher % inhibition associated with expected antiplatelet effect.
		Presurgical - <20% inhibition
PHONE	PHONED	(PHONED TO TONIA AT 0916 ON 12/29. FAXED.)

Platelet Reactivity P2Y12 – 270(194-418) – this indicates the amount of ADP-mediated aggregation specific to the platelet P2Y12 receptor. This provides the extent of platelet aggregation in the presence of clopidogrel.

PLT FUNCT BASE - 326 (194-418) –The BASE result serves as an estimate of baseline platelet function independent of P2Y12 receptor inhibition. The BASE estimates the total possible platelet aggregation regardless of the presence of clopidogrel.

P2Y12 INHIBITION - (17) (presurgical <20%) – this is the percent change from baseline aggregation, and is calculated from the PRU result and the BASE result.

Bale/Doneen: Upcoming meetings

- American Academy of Oral Systemic Health
  - June 24-25: Chicago,
- CHL dinner lecture
  - July 14: Chicago
- BHL 5 hr Saturday Program
  - July 16: West Palm Beach Florida
- BHL 5 hr Saturday Program
  - August 20: Charleston SC
- Bale/Doneen CME Preceptorship Program
  - August 26-27: Chicago, IL
- Cleveland HeartLab & Bale/Doneen Reunion
  - September 15-17: Cleveland, OH

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