New Advances in Heart Attack & Stroke Prevention: A Guarantee for Arterial Wellness

2014 TOMA & TXACOFP Annual Convention

June 7, 2014

Bradley F Bale, MD

Outline

- Past, Present, Future: Heart Attack & Stroke Care
- Sub-clinical arterial disease
- Inflammation as causal
- Bio-markers of inflammation
- Plethora of conditions generating arterial inflammation
- Management to extinguish inflammation
- Graphic cases
- Q & A

AHA 2013 Statistics

Approx. every 34 seconds, an American will have a heart attack.

Approx. every minute someone will die from a heart attack.

AHA 2013 Statistics

Average age of first heart attack is 64.5 yrs/men and 70.3 yrs/women.

Average number of years of life lost because of a heart attack is 16.6.


Sudden Cardiac Death (SCD) Most Costly Health Condition

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

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


SCD: Societal burden is high!

• Total years of productive life lost (YPLL) from SCD for men ~ 2.04 million (95% uncertainty interval, 1.86–2.23 million)

• Total YPLL from SCD for women ~1.29 million (95% uncertainty interval, 1.13–1.45 million)

CAD Causes the Vast Majority of Sudden Cardiac Death


SCD: What do they propose as a solution??

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

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


AHA 2013 Statistics

Every 40 seconds, someone in the United States has a stroke.

23% are recidivistic!

Every 4 minutes someone dies from a stroke

Proportion of patients with **recurrent stroke** within 5 years after first stroke.

Women should be upset!!!

Direct and indirect costs of cardiovascular disease (CVD) and stroke (in billions of dollars), United States, 2010.

Total = $315.3 billion

Projected total costs of cardiovascular disease (CVD), 2015 to **2030** (2012 $ in billions) in the United States.

= $1.2 trillion
Question #1: Why is the current ‘risk factor’ paradigm innately flawed?

What has to be present to have an ischemic event?

a) Traditional risk factors
b) Atherosclerosis
c) Both

Prevalence of Major Risk Factors in Heart Attacks

Heart Attacks
Coronary atherosclerosis essentially is a \textit{conditio sine qua non}.

Therefore, assessing its extent, severity, and location must be considered fundamental for risk estimates.


Question #2: What type of atherosclerosis causes most heart attacks??

a) >70% obstructing plaque
b) 50-70% obstructing plaque
c) <50% obstructing plaque

Event Reality: Most Heart Attacks are Caused by Non-obstructing Plaque

<table>
<thead>
<tr>
<th>Pre-MI Stenosis</th>
<th># Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70%</td>
<td>14%</td>
</tr>
<tr>
<td>50-70%</td>
<td>16%</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>68%</td>
</tr>
</tbody>
</table>

86% of MIs are from plaque <70% obstructing
68% of MIs are from plaque <50% obstructing
Silent potentially deadly plaque!

Histology of vulnerable coronary plaques seen on Movat’s pentachrome staining. (A) Plaque leads to concentric luminal narrowing; the asterisk (*) indicates a focal area of lipid accumulation and the overlying cap is thin. Of note, the preserved luminal area causes detection difficulties for coronary angiography and other forms of lumography. (B) A higher-magnification image of the boxed area in A showing the lipid pool (*) and thin fibrous cap (arrow) more clearly.

Nature Clinical Practice 3/06, Vol 3, NO 3:155

Do We Have the Technology to Identify This Type of Coronary Atherosclerosis?

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Calcium in Arteries

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Coronary Artery Calcification (CAC)

CAC documents presence of coronary ASVD

2A recommendation by the ACC/AHA to refine the CV risk assessment.


Do Current Studies Support Utilizing This Technology to Define CV Risk?

CAC Out Predicts Lipids for CVD Risk

- 5,534 MESA pts without baseline statin rx; follow-up 7.6 yrs.; outcome CV events.

- Classified pts by CACS of zero; 1-99; >100; # lipid abnormalities (LA).

- Which paradigm of risk assessment is superior?: dyslipidemia (risk factor) and CAC (atherosclerosis).

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not number of lipid abnormalities

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CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not by LDL-C

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CAC predicts stroke risk

- 4180 pts: 45-75 yo; 47.1% men; without known CVD; baseline CACS; evaluated for stroke events ~ 8 yrs.
- 92 strokes; 55 men & 37 women; 82 ischemic and 10 hemorrhagic

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CAC predicts stroke risk


CAC Out Predicts Lipids for CVD Risk

Atherosclerosis is superior to risk factors for predicting CV events.


Arterial Disease in Any Vascular Bed Predicts CV Event Risk

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Any 1 system</th>
<th>CAD alone</th>
<th>CVD alone</th>
<th>PAD alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n =</td>
<td>42,716</td>
<td>28,867</td>
<td>10,603</td>
<td>3,246</td>
</tr>
<tr>
<td>CV death, MI, or stroke (%)</td>
<td>4.07</td>
<td>3.64</td>
<td>5.54</td>
<td>3.06</td>
</tr>
</tbody>
</table>

One-year Outcomes for Patients with Arterial Disease at One or More Sites

Data from over 68,000 pts. from 44 countries; real practices

IMT of Carotid (CIMT)  
American Heart Association  
safe, non-invasive, inexpensive, valid and reliable

AHA Expert Panel Statement of Prevention V  
Conference - Circulation 2000

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Carotid Ultrasound Test


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Limited Commentary

Appropriate use criteria for carotid intima media thickness testing

The Society of Atherosclerosis Imaging and Prevention. Developed in collaboration with the International Atherosclerosis Society

Writing group: Allen Taylor, Mark Oldendorf, Mario DeMichelle, Amy Doneen, Dale Faulkner, Kim Sutten-Tymel

SAIP Council, Atherosclerosis 10/19/2010

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Carotid Intima-Media Thickness Testing as a Clinical Tool

Clarify clinical utility for risk assessment

Discuss the usefulness in treatment decisions


CIMT Strongly Predicts Heart Attack (MI) Risk

6,257 ‘healthy’ 25-84 yo: 52% women; followed 15 ½ yrs.; evaluated CIMT as predictor of MI

CIMT categorized as quartiles of IMT and total plaque area

894 incident MIs


CIMT Strongly Predicts Heart Attack Risk

MI risk increased significantly across quartiles of mean intima-media thickness (P for trend <0.001) and with increasing total plaque area (P for trend <0.001).

Carotid atherosclerosis was strongly associated with future MI.

Does Carotid ASVD Predict Stroke Risk?

CIMT Predicts Ischemic Stroke

The presence of Internal carotid artery plaque > 1.5 mm was a significant independent predictor of stroke.


CCA IMT Progression Predicts Stroke Risk

5,028 MESA subjects; followed 3 yrs; average age 64; 52% female

IMT rate of change significantly associated with incident stroke HR - 1.23 per 0.05 mm/year (95%CI, 1.02–1.48)

Other Ways to Detect Subclinical ASVD?

Other Imaging Reports
- Dental x-rays – calcified arteries
- Mammograms – calcified arteries
- Extremity x-rays – calcified arteries
- CXR – calcified arteries
- Abd x-rays – calcified arteries
- Cerebral images – calcified arteries
- Carotid duplex – stenosis; plaque
- Abd US – thrombosis in aorta
- Retinal scanning – atherosclerotic lesions

Question # 3
Most people between 35 and 65 yo will have carotid or femoral plaque?
- True-
- False-

If plaque is found, it should be treated?
- True-
- False-
Sub-clinical Atherosclerosis Predicts CV Risk

- 10,000 healthy subjects followed 10 yrs.; 40% female; aged 35-65 yo; base line B-mode US carotids and femorals

- No treatment allowed over 10 years -
  - Class 1 (normal artery): 7989 subjects
  - Class 2 (wall thickening): 930 subjects
  - Class 3 (disease present): 611 subjects
  - Class 4 (stenotic disease): 470 subjects

- ~90% did NOT have plaque!


The Risk of Not Treating Plaque

Virchow 157 Years Ago Proposed Inflammation as Cause of Atherosclerosis
Atherosclerosis (ASVD) is an Inflammatory Disease

The earliest lesion is a pure inflammatory lesion.


Inflammation Drives Arterial Disease

Inflammation plays a key role in the development and progression of atherosclerosis. Inflammation destabilizes plaque and promotes thrombosis.


Inflammation is Causal

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- 60,608 subjects; 10,668 with CHD; genetic study
- Investigate if remnant cholesterol & or LDL are inflammatory.
  (Remnant cholesterol is very low-density lipoproteins (VLDL) and IDL also includes chylomicron remnants in the non-fasting state.)


Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

Remnant cholesterol is inflammatory & 39 mg/dL higher level of non-fasting remnant cholesterol increased the risk of heart attack 3.3 X (95%CI: 2.1-5.2).

LDL was not inflammatory until it is oxidized & 39 mg/dL higher level of LDL-C increased heart attack risk 1.8X (95%CI: 1.5-2.2).


Lipo (a) Causes Heart Attacks

Copenhagen Data: >41,000 subjects over 13 years, 2800 MIs

Looked at risk of MI from lipo (a) levels by assessing the levels genetically

Consistent increase in MI risk with higher lipo (a) levels

Risk starts around 40-50 mg/L; each doubling of the level increases the risk about 20%

Dr Pia R Kamstrup, PR, et. Al., JAMA 6/10/09
Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- 7,730 white Jupiter pts; median lipo (a) of 23 nmol/L at baseline; evaluated baseline and on-rx lipo (a) as independent risk for CVE.

- The median change in Lp(a) with rosuvastatin and placebo was zero.


Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

Despite potent statin therapy with achievement of very low LDL cholesterol (median on-treatment LDL cholesterol 54 mg/dL), baseline and on-statin Lp(a) concentrations were associated with residual risk of CVD independent of other risk factors, including LDL cholesterol.


Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- Pts whose on-statin Lp(a) was >50 mg/dL.

HR-1.67; (95% CI, 0.93~3.02) P=0.09

Smoking: Inflammation

Cigarette smoke provokes an increase in the expression of pro-inflammatory cytokines (including IL-6, TNFα and IL-1β).


Anxiety Increases Arterial Inflammation

- 280 ACS pts; rated anxiety level; intense anxiety in 21.6%; moderate 66.1%
- Level of anxiety was positively associated with plasma TNFα on admission after controlling for sociodemographic factors, clinical risk, and pain intensity. High versus low:
  \[ \text{OR} = 4.67 \ (95\% \ C.I. \ 1.66–12.65) \ p=0.005 \]


Anxiety Increases Arterial Inflammation

Proportion of pts with tumor necrosis factor alpha values ≥ 12 pg/ml, reporting low, moderate, or intense distress and fear of dying. Values are adjusted for age, gender, ethnicity, marital status, social deprivation, statin use on admission, GRACE score, number of days in hospital, and pain intensity.

Pre-diabetes Damages Arteries

“My brother caught diabetes when he was in the hospital for his heart attack.”


Insulin Resistance Increases Arterial Inflammation

- Carotid inflammation assessed with FDG-PET
- 90 pts: 30 normal GTT; 30 impaired GTT; 30 T2DM
- Inflammation significantly increased with impaired GTT and T2DM


Sleep Loss Generates Inflammation

Review of studies from 2002-2013

Deficient sleep is pro-inflammatory making it a risk factor for CV, metabolic, and neurodegenerative diseases.

PD Directly Linked to Atherosclerotic Inflammation

- 112 pts underwent FDG (F-fluorodeoxyglucose)-PET
- Assessed target-to-background ratios (TBR); the periodontal FDG uptake was associated with carotid FDG uptake ($R=0.64, p<0.001$) and aortic uptake ($R=0.38, p<0.029$).
- 16 pts had carotid endarterectomies: strong relationship between periodontal TBR and histologically assessed inflammation within carotid plaques ($R=0.81, p<0.001$).


Level A evidence that PD is independently associated with arterial disease.


Oral Pathogens and Acute Heart Attack

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

Pessi, T., PhD, et. al. Circulation. published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.01254
Oral Pathogens and Acute Heart Attack

Electron microscopy performed on 9 thrombi
Bacteria-like structures detected in all 9; whole bacteria in 3/9

Oral Pathogens and Acute Heart Attack
- 30 pts had panoramic CT imaging
- ~50% showed periapical abscess
- If pt’s thrombus was positive for strep viridans DNA, they were 13 times more likely to have a periapical abscess
  \[ \text{OR } 13.2 \ (95\% \ CI \ 2.11 - 82.5) \ p=0.004 \]

Oral Pathogens and Acute Heart Attack: Conclusions
- Dental infection and oral bacteria are associated with the development of acute coronary thrombosis – heart attack!!!
- Dental health and dental care should be one major element in preventing heart attacks!!!
Risk of CV Death/MI or Stroke Increase with hs-CRP levels of > 1mg/L

<table>
<thead>
<tr>
<th>hs-CRP level</th>
<th>Hazard ratio of CV death/MI/stroke (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 mg/L</td>
<td>1.39 (1.06–1.81)</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>1.52 (1.15–2.02)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Adjusted for baseline characteristics and treatments
3771 stable CAD pts. followed 4.8 yrs.; 400 major events


Microalbumin/Creatinine Ratio (MACR) Independently Predicts Risk of CV Events

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Adjusted hazard ratio per 1 SD increment in the log value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACR</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Framingham data; 3208 pts.; followed 7.4 yrs.; 207 deaths

Eight markers not predictive: CRP, N-terminal proatrial NP, aldosterone, fibrinogen, D-dimer, PAI-1, renin, homocysteine

Bottom line: MACR trumps hsCRP and fibrinogen


MACR Cut Points for Marking Increased CV Risk

Risk when MACR > 7.5 in women and > 4.0 in men

<table>
<thead>
<tr>
<th>End point</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>2.92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fram. Offspring healthy pts.; mean age 55; 58% women followed 6 yrs.

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

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


Lp-PLA2 Increases in Inflammatory Macrophages in Vitro

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


Lp-PLA2 Increases During Differentiation of Human Monocytes to Macrophages In Vitro
Lp-PLA2 Increases in ‘Foam Cells’ in Vitro

- Macrophages exposed to oxidized LDL-C for 48 hrs
- Induced ‘foam cell’ production


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

The lack of in vivo increase in plasma or monocyte levels of Lp-PLA2 during acute inflammation coupled with this data suggests that, in human atherosclerosis, Lp-PLA2 may be generated by macrophages and foam cells rather than by circulating leukocytes. Lp-PLA2 is not an acute phase reactant.


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

Regardless of other known risk factors!

Cases

History
10/2007; 44 yo white male
Reason for visit: Keep wife happy; Father - stroke at 58yo and heart attack; Maternal grandfather died of heart attack at 60 yo.
Meds: none
Habits: excellent
ROS: migraine HA
Sochx: Happily married; own successful company

Physical
Vital signs: Ht.- 6’ 1”; Wt.- 186 lbs.; BMI – 24.5; Waist- 33 in.; BP-120/72; pulse- 60; RR-16
Exam - normal
Standard Labs

Lipids (without rx):
- TC-187; TG-94; HDL-47; LDL-121
- FBS-83; Creat. – 1.1 with eGFR-77; CMP –wnl normal
- Thyroid – normal
- CBC: WBC – 4.7 with normal diff.; H&H – 16.8/47.1

Standard of Care to Determine CV Risk and Potential Need for Therapy

- FRS – 1%
  - ATP III – 1% with ≤1 risk factor = low risk and LDL goal of <160 mg/dL
- Reynolds’ Risk Score for men which includes hs-CRP (1.6 mg/L) and family history: = 3% risk

Lipid Therapy Guidelines 12/12/2013

High-moderate intensity statin rx for all of the following:

a) ‘Secondary’ prevention – proven ASVD due to an event or need for an intervention. High intensity

b) LDL-C ≥190 mg/dL – High intensity

c) Diabetic 40-75yo with LDL-C ≥70mg/dL (‘primary’) – moderate intensity; if 10 yr. risk ≥7.5% - High intens.

d) ‘Primary’ prevention with LDL-C ≥70mg/dL & 10 yr. risk ≥7.5% - high or moderate intensity

Lipid Therapy Guidelines 12/12/2013

State: If statin not indicated with one of the four criteria, may consider additional factors influencing ASCVD risk.

a) LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias
b) Fam hx: first degree relative with ASCVD <55yo male or <65yo female
c) hsCRP >2 mg/L
d) ankle-brachial index <0.9
e) elevated lifetime risk of ASCVD


Standard of Care: Conclusions

Congratulations!!!
Low risk.
No therapy needed.
Wise husband.
Wife overly cautious!!

Inflammatory Labs Added!

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>TC</td>
<td>187</td>
</tr>
<tr>
<td>TG</td>
<td>94</td>
</tr>
<tr>
<td>NDL</td>
<td>47</td>
</tr>
<tr>
<td>LDL</td>
<td>121</td>
</tr>
<tr>
<td>Lipo(a)</td>
<td>6</td>
</tr>
<tr>
<td>ApoB</td>
<td>90</td>
</tr>
<tr>
<td>Creat.</td>
<td>1.1</td>
</tr>
<tr>
<td>FBS/OGTT</td>
<td>87/74</td>
</tr>
<tr>
<td>A1c</td>
<td>4.2</td>
</tr>
<tr>
<td>TSH</td>
<td>2.7</td>
</tr>
<tr>
<td>hsCRP</td>
<td>!!!!!</td>
</tr>
<tr>
<td>MPO</td>
<td>!!!!!</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>!!!!!</td>
</tr>
<tr>
<td>Power</td>
<td>!!!!!</td>
</tr>
</tbody>
</table>

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BD Method to Determine Risk

- Educate: Atheroma ‘cat in gutter’ is prerequisite; usually asymptomatic until obstructing thrombus; arterial inflammation causal

- Disease:
  1) review his record for evidence of atheromas—
  2) recommend CIMT to look for atheroma

2.6 mm soft ICA in left carotid
3.0 mm soft bulb in left carotid

Single maximum IMT value as predictor of stroke

<table>
<thead>
<tr>
<th>Carotid</th>
<th>IMT mm</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>2.33</td>
<td>1.69 – 2.96</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>2.45</td>
<td>1.97 – 2.93</td>
</tr>
<tr>
<td>Internal</td>
<td>2.33</td>
<td>1.83 – 2.84</td>
</tr>
</tbody>
</table>

Based on 55 consecutive pts. who had endarterectomy following an event & 24 pts. who died from non-cerebrovascular disease
56yo to 79yo, approx. 1:1 female
Internal carotid was best at identifying at risk individuals
Mario De Michele, Daniel J. Zaccaro, Gene Bond
*Nutrition, Metabolism & CVD* (2006) 16, 536 - 542
Conclusions

"Wes, your wife is right (she usually is). You have arterial disease. You have risk for an event. Nice to find on paper. Therapy can prevent an event. Go home and hug wife and sons!

One Yr Rx: rosuvastatin 10mg; ASA 81mg; omega 3 1 gr.

- TC 187
- TG 94
- HDL 47
- LDL 121
- Lipid (a) 6
- ApoB 90
- TC:HDL 3.9
- Creat. 1.1
- Alt/Ast 32/31
- FBS/OGTT 87/74
- A1c 4.2
- TSH 2.7
- hsCRP 1.6
- MAC 1.1
- Lp-PLA2 156
- MPO 834

Lipids great! good to go?

Is Superman Fine??

- Standard of care- he is.
- BD Method- very concerned; look at disease.
Inflammation is the Driver not Cholesterol

<table>
<thead>
<tr>
<th></th>
<th>10/07</th>
<th>11/08</th>
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<tbody>
<tr>
<td>Average CCA mean IMT mm</td>
<td>0.77</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>62yo</td>
<td>70yo</td>
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<tr>
<td>Average CCA max IMT</td>
<td>0.81</td>
<td>0.94</td>
</tr>
<tr>
<td>Plaque size mm</td>
<td>3.0 S</td>
<td>3.5 S</td>
</tr>
<tr>
<td></td>
<td>2.6 S</td>
<td>2.8 S</td>
</tr>
</tbody>
</table>

CCA IMT Progression Predicts Stroke Risk

- 5,028 MESA subjects; followed 3 years
- Every 0.05 mm/yr increase in CCA IMT = 23% risk increase
  HR - (95%CI, 1.02–1.48)

**Yikes!! -0.08 mm increase = 37% increase risk of stroke!**

<table>
<thead>
<tr>
<th>Test</th>
<th>11/07</th>
<th>11/08</th>
<th>11/09</th>
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<tbody>
<tr>
<td>Mean CCA IMT mm</td>
<td>0.77</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean max CCA MT mm</td>
<td>0.81</td>
<td>0.94</td>
<td>0.89</td>
</tr>
<tr>
<td>Plaque size mm; echo</td>
<td>3.0 S</td>
<td>3.5 S</td>
<td>2.7 H</td>
</tr>
<tr>
<td></td>
<td>2.6 S</td>
<td>2.8 S</td>
<td>2.3 H</td>
</tr>
</tbody>
</table>

[2 Yrs Rx: rosuva10mg; ASA; omega 3; ER niacin 500mg]

<table>
<thead>
<tr>
<th>Lipids</th>
<th>2 Yrs</th>
<th>3 Yrs</th>
<th>4 Yrs</th>
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<tbody>
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<td>134</td>
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<tr>
<td>TG</td>
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<td>LDL</td>
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<tr>
<td>TC:HDL</td>
<td>3.9</td>
<td>3.2</td>
<td>2.6</td>
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<td>0.9</td>
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<tr>
<td>InsCRP</td>
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<td>0.8</td>
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<tr>
<td>MACR</td>
<td>7.1</td>
<td>7.8</td>
<td>2.3</td>
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<tr>
<td>Lp-PLA2</td>
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<tr>
<td>MPO</td>
<td>834</td>
<td>786</td>
<td>350</td>
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</table>

Lipids still great!

Fire is out!
<table>
<thead>
<tr>
<th>Date</th>
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Lipids still great!

Fire rekindling?
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- Lipids getting borderline!
- What is going on!!!
- Fire getting hotter!

Twice a daily mouth 'car' wash & oral care

- CloSYS Rinse 30 sec
- Sonicare Brush with xylitol toothpaste
- Floss (xylitol)
- Listerine Rinse 30 sec.
- Act Rinse 1 minute
- Using xylitol gum and mints throughout the day after ingesting anything acidic.
61 yo Caucasian Male

- 2008 at age 56 - severe angina - CABG with 5 graphs

- Remained under care of cardiologist

- 8/2012 at age 60- major heart attack —4 of 5 graphs totally occluded; received 3 stents

- Mild heart failure - 12/2012 finds out about Bale/Doneen Method
61 yo Caucasian Male: seen 1/2013

- Asked why he has arterial disease – he has no idea; only issue has been mild cholesterol elevation; told he is definitely not pre-diabetic; quit smoking 39 years ago & only smoked 2 yrs; BP always good; minister with no significant stress; diet and physical activity okay; no soda pop; no dental complaints; flosses some; snores, if does not wear dental device

- Famhx: Mother had coronary, peripheral and cerebral arterial disease – died stroke at 56 yo; Maternal grandmother died stroke at 65 yo; Maternal grandfather died stroke at 72 yo. Maternal uncle died type 2 diabetes at 62 yo

61 yo Caucasian Male: seen 1/2013

- BP – 117/77; Ht. 5’ 7”; Wt. 166 lbs.; waist 36”; BMI – 26

- Meds: ASA 325mg; clopidogrel 75mg; atorvastatin 40mg; metoprolol 25mg

- CV exam; unable to detect pulses in top of foot

- Oral exam – negative to my untrained eyes!!!!- just wait!

- ABI + for PAD on right with score of 0.90

- CIMT – 1.8 mm H bifur. right; 3.1 mm H bifur. left

61 yo Caucasian Male

Labs 01/2013: lipids

- TC - 214
- TG - 236
- HDL - 37
- LDL - 130
- TC/HDL - 5.8
- TG/HDL - 6.4
- apoB-132
- LDL 3a&3b- 45%
- HDL2b- 15%
- lipo (a) - 179

This is a full house!!!
Slight cholesterol issue???
61 yo Caucasian Male
Labs 01/2013: inflammation
- hsCRP - 6.3
- MPO – 446
- PLAC-2 – 148
- MACR- <4.0
- F2 isoprostane -0.37
- Bilirubin – 0.3

61 yo Caucasian Male
Labs 01/2013: insulin resistance
- GGT- 126 (>47)
- Alt-35 (>34)  He was told he is not pre-diabetic!
- Insulin- 11
- FBG – 87 mg/dL
- A1c- 5.4%
- 2 hr. glucose 139 mg/dL
- 1 hr. glucose 146 mg/dL
- TG/HDL – 6.4
- Metabolic syndrome – (HDL, TG, BP)

Abnormal 2 hr. Glucose Identifies IR and Defines Beta cell Function Loss

DeFronzo, R. Diabetes, Vol. 58, April 2009
61 yo Caucasian Male
Labs 01/2013: misc.
- Vit. D - 32
- NT – proBNP – 240 (want < 125)
- Heterozygous for 9p21
- CoQ-10 – 0.32
- Homocysteine- 7.6
- Thyroid- normal
- Testosterone- normal
- Ferritin- normal
- Apo E 3/3
- KIF6; LPA; CYP 2C19- negative

61 yo Caucasian Male: Diagnosis
- Severe CHD post CABG & MI with mild heart failure
- Significant subclinical carotid ASVD* – high risk for stroke
- PAD*
- Complicated hyperlipidemia of IR with lipo (a)*
- Hypertension
- Pre-diabetes – IR*
- Sleep disorder
- Borderline low vit. D*
- 9p21 heterzygous*
- Famhx ASVD
- PD*
- Low CoQ-10*
- Low bilirubin*

*All new diagnosis from the Bale/Doneen Method
Individual Management

- Lifestyle: exercise minimum 22 mins./day; d/c red meat, fried foods; eat fish 5X/week; BHL consult; music; laugh; wear dental device at night
- Decrease ASA to 81mg
- Fish oil 4 grams/d
- CoQ 10- 200mg/d
- Vit. D3 – 1,000 IU/d
- Dark chocolate 7 gr/d
- Cinnamon 2 gr/d with chromium
- Vaccines: flu, pneumonia, shingles
- L-carnitine 2 gr/d; metamucil daily

Individual Management

- ramipril 2.5mg q evening; try to work up to 10mg
- d/c atorvastatin 40mg; wait 48 hrs.; start rosuvastatin 20mg/d

61 yo Caucasian Male: seen by Dr. Clarence Feller 2/2013

- Non vital teeth: 7,8,9,10
- Enamel damage with dentin exposure teeth: 18,19,30,32,22-27
- PD exam: moderate gingival inflammation; multiple 4 & 5 mm pockets with bleeding in all 4 quadrants
- Decay in teeth 3 & 5; pus lingual side tooth 4; large decay tooth 14 with communication to failing root canal tooth 4
- Tooth 32 in horizontal impaction with pus in medial pocket
- Tooth 14 mesial root communicating with sinus
- Bilateral sinus involvement
CT Images Taken by Dr. Clarence Feller  
2/27/2013: sinus involvement

Fast Forward to 3/13/2014: Clinical Visit
Lifestyle: 1) diet – fish everyday; no red meat since 1st visit; lots more fruit and veggies 2) exercise – improved, but still not everyday & used weather excuse! 3) wt. – lost 6 lbs right away and kept it off – 165 lbs. 4) sleep – 7 good hours 5) oral health – sees hygienist and dentist q 3mos. 6) stress not an issue ☺
Antiplatelet rx: clopidogrel 75mg & aspirin 81mg
Statin: rosuvastatin 20mg
RAAS: ramipril 2.5mg each evening
Beta-blocker: carvedilol 3.125mg bid
Plus: endurance 1500mg qd; fish oil 4 gram/d; vit. D3 1,000 IU; dark chocolate 7 gr/d; cinnamon 2 gr/d; coffee 3/d

Fast Forward to 3/13/2014: Clinical Visit
BP -112/70 waist 37 inches P-58 & reg RR-16 R&R
Exam: neg

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Inflammation- excellent= low risk
Oral infections – managed
IR – stable
HF – greatly improved
Renal function- excellent
Hepatic function- excellent
CoQ10- corrected
Vit D- improved
Diet improved
Sleep improved
Exercise improved
Low bilirubin improved
Hypertension – optimal
Hyperlipidemia – basics optimal & lipo (a) much better

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ABI: 2/13- 0.90; 3/14- 1.03