A Message from your Heart; Answers for Cardiovascular Disease
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Calcium Score Progression
the Paradigm Shift in Cardiology

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Financial Disclosure:
None to Report

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Coronary Artery Calcification
What Good is It?

Egyptian Princess Ahmose-Meryet-Amon, 1550 BC.

Coronal CAT – Three Vessel CAD

4 Different Ancient Cultures Studied

Not a Post-Industrial Disease


Case Report
The Power of Zero

55 Y/O Female On Statins for Cholesterol of 235
Advised to D/C Statin, Cardiologist Re-Starts.
Do a Calcium Score to Determine Risk.

**Calcium Score = Zero  (Asymptomatic ! )**

Cardiologist Agrees to **STOP** Statin.
Statins Have No Clinical Benefit for CAC=0 (Mitchell,2018)

Imaging Atherosclerotic Disease

Imaging with SPECT Perfusion, CT-Angio and Cath Angiography
CAT Scan
Coronary Artery Calcification

Calcified LAD.
Quantify Calcium
Agatson Score

Paradigm Shift

Serum Cholesterol

Calciun Score
1) Cholesterol Theory has been Falsified and
2) Replaced by LPS Theory of Heart Disease.
3) Endotoxemia from Leaky Gut and Periodontal Disease, ^ NFKB and Seeds Atherosclerotic Plaque.
4) Plaque is Infected Bio-Film with ^ NFKB.
5) Calcification is Inflammatory Response to Infection.
6) Calcium Score  Annual Progression: Powerful Predictor of Impaired Survival, MI, Statin Failure.
7) Statin Benefits: All Due to Pleotropic Effects, Not Cholesterol Lowering.
8) Integrative Protocols to Slow Progression of CAC.
9) Future Research: Third Integrative Arm Raggi Study.
LDL Cholesterol Causes Atherosclerosis

Falsified

“The More LDL There is in the Blood, the More Rapidly Atherosclerosis Develops.” 1984

Michael Brown and Joseph Goldstein, Nobel Prize Physiology and Medicine for Discovery of the LDL Receptor, 1985.

“The More LDL There is in the Blood, the More Rapidly Atherosclerosis Develops.”

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Cholesterol Theory Falsified Summary

1) Calcium Score - **No Correlation** between Cholesterol level and Calcium Score. (Harvey Hecht, 2001)

2) Autopsy Studies: **No Correlation**: Cholesterol and Atherosclerotic Plaque. (Ware, 2009)

3) 2004 Raggi Study: 495 pts on Statins: 41 Heart Attacks Over 6 Years – **No Difference** in Cholesterol. (Raggi, 2004)

4) CETP Inhibitor Evacetrapib: Lowers LDL - **Failed** Clinical Trials. (Lincoff, 2017)

5) Familial Hyper-Cholesterol: 40% w/ **NO CAD** Simon Broome Registry (Neil Andrew, 2008)

6) Reverse Epidemiology/Cholesterol Paradox: Dialysis, CHF, RA, COPD, and Elderly, High Cholesterol Improves Survival. (Horwich, 2007)

References Cholesterol Theory Falsified


Ware, William R. “The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.” Med Hypotheses 73.4 (2009): 596

Cholesterol Does **NOT** Cause Vascular Calcification

- 2001 - Calcium Score Study (EBT)
- **Non-Correlation**

This Disproves the Hypothesis that Cholesterol Causes Vascular Calcification.

Autopsy Studies – No Correlation Between Cholesterol and Atherosclerosis Severity

“No relationship was present in any age group. It is concluded that the incidence and severity of atherosclerosis in man is not directly correlated with the blood serum cholesterol content.” -(Lande, 1936)

“No correlation could be observed between the serum cholesterol level and the amount and severity of atherosclerosis in the arteries.” (Mathur, 1961)

Non-Statin Lipid Lowering Failure
Evacetrapib - CETP

- Cholesteryl Ester Transfer Protein Inhibitor
- 2 Year Multicenter, Randomized, Double-blind, Placebo-Controlled Trial
- 12,092 Patients w/High Risk for CAD.
- Reduced LDL 31%, Increased HDL 131%

No Reduction in Rate of Cardiovascular Events compared to Placebo.

This Proves that Statin Benefits are Due to Pleotrophic Effects, NOT Cholesterol Lowering.

Falsifying the Cholesterol Theory
Zero CAC – Lifelong Cholesterol 580

72 y/o old Male
Untreated Familial Hi-Cholesterol Level = 580
LDL = 480 mg/dl.
Calcium Score of ....... Zero
No Heart Disease

The Endotoxin-Lipoprotein Hypothesis

- Lipoproteins Bind and Neutralize Circulating Endotoxin, (Sandek, 2007)
- If **LPS** causes **CAD**, Then Higher Cholesterol is Protective.
- Explains Reverse Epidemiology

Atherosclerotic Plaque
What is it?

Activated NF-Kb
Calcification
And More
Atherosclerotic Plaque – Activated NF-KB


LPS Activates NF-KB, IL-6, TNFa

LPS recognized by Toll Receptor on Surface Membrane of Macrophage, then activates NFKB, Enters Nucleus, Induces IL6 and TNF-alpha, which drives vascular calcification.

Proposed mechanisms for anti-inflammatory in LPS-induced macrophages.

Arterial Calcification Stains Green

Doherty, Terence "Molecular, endocrine, mechanisms of arterial calcification." Endocrine reviews 25.4 (2004): 629-672. In some cases arteries can evolve into mature bone tissue histomorphologically indistinguishable from skeletal bone.
Evolution of Atheroma Plaque – Mainstream

Evolution of Calcified Atheroma Plaque

Osteoblast-Like Cells

Calcification

“Vascular Calcification is a Clinical Marker for Atherosclerosis”.


Chronic Inflammatory Focus = Infection.

Examples of Soft Tissue Calcification Surrounding Chronic Inflammatory Foci = Infection
Cysticercosis

What is the Evidence for Infection in Atherosclerotic Plaque?
Atherosclerotic Plaque is Poly-Microbial Biofilm

Ribosome RNA

Plaque is Infected Biofilm

16s Ribosome RNA, FISH Technique

Atherosclerotic Plaque Samples

Atherosclerotic Plaque is Infected Biofilm Colonized by Bacterial, Fungal and Protozoal Organisms.


Plaque is Infected Biofilm

Cultivation of Micro-Organisms from Diseased Tissue has been Demonstrated

Atherosclerotic Plaque as Polymicrobial Infected Biofilm

Interventions for Infected Biofilm

Garlic - Disrupts Quorum Sensing
EDTA
Proteolytic Enzymes
Reactive Oxygen (Ozone)

Delgado-Roche "Ozone oxidative preconditioning prevents atherosclerosis development in New Zealand white rabbits." J Cardiovasc Pharm 2013
Bacterially-Derived Signals Drive Cardio-Metabolic Diseases.

Intestinal Origin of Bacteria in CAD

Intestinal Bacterial by 16S rRNA Detected in Both Blood and Atherosclerotic Plaque of 16 Patients. (Li, 2016)

Intestinal Bacteria in Plaques may Originate from Intestine.

Higher Zonulin Levels (Doubled) in CAD Patients

Peri-Odontal Origin of Bacteria in CAD

Mouse Model: Sequential Colonization of Peri-Odontal Pathogens to Distant Organs (heart)
Humans: Linkage - Oral Bacteria and Plaque Bacteria in CAD patients. (Chhibber, 2016)

Atherosclerotic Plaque as Poly-Microbial Infected Biofilm

Review of Literature:
63 Studies and 23 Bacteria in Human Atherosclerotic Plaque Samples.
Links Oral Bacteria to Plaque Bacteria.

Calcium Score – We Are Looking At the Actual Disease

Caution with Calcium Score
Symptomatic vs. Asymptomatic

Asymptomatic Patients: Calcium Score Useful Here.

Symptomatic Patients: w/ Angina, Proceed to CT-Angio or SPECT Perfusion Scan Regardless of Low Calcium Score.

Baseline Calcium Score
Powerful Predictor of Impaired Survival

CAC Progression Paradigm Shift
Paolo Raggi – 2004 - Annual CAC

- 495 Asymptomatic Pts.
- All On Statins After First EBT Scan.
- No History CAD, Stent or CABG.
- F/U Calcium Score Every 2 Yrs.
- 41 MI’s over 6 years.
- Mean LDL Did Not Differ !!!
- 118 vs. 122 mg/dL, (MI versus Non-MI)

Why Did 41 Patients on Statins Have CAC Progression and MI?

Pleiotropic Effects Overwhelmed by Severe Endotoxemia.
CAC progression of <15% per year is associated with a benign prognosis.
Harvey S. Hecht  JACC: Cardiovascular Imaging Volume 8, Issue 5, May 2015
4,609 Asymptomatic Referred by Primary for CAC.

All Cause Mortality Data.

Fig 2 Budoff, Matthew “Progression of coronary artery calcium predicts all-cause mortality” JACC: Cardiovascular Imaging 2010
Progression of CAC: What Does it Mean?

- Progression of Calcification Means Active Disease in the Arterial Wall. (Infection and Inflammation)
- 17-Fold Increased Risk of MI.
- Non-Progression: In-Active or Healed Disease, Low Risk for MI.

Budoff, Matthew “Progression of coronary artery calcium predicts all-cause mortality” JACC: Cardiovascular Imaging 2010
Statins for Calcium Score?

Statins Actually Enhance Progression of Vascular Calcification. (Dykun, 2016)

Depletion of Vitamin K2 with Statins.

Statins Improve Survival in Sepsis and Pneumonia. (Hennessy, 2016)

Statins Improve Survival in Pts Undergoing Bypass Surgery: 50-70%. (Curtis 2017) (Barakat 2016)

Statins Pleiotrophic Effects
In-Vitro Studies

- Suppresses LPS Signaling in Monocytes (Patel, 2004)
- Blocks LPS -Release of IL-6 and TNF-Alpha. Decreases Nuclear Factor-KappaB. (Devaraj, 2006)
- Prevents TNF-Alpha-Induced NF-KappaB Activation and Gene Transcription in Cultured EC. (Hölschermann, 2006)


Repurposing Statins as Novel Antimicrobials?

in vitro  cell culture  in vivo

A. In vitro
- Control
- Statin
- Growth
- Control
- Statin
- Motility
- Control
- Statin
- Early/established biofilms

B. Cell culture
- Bacterial toxins
- Invasion
- Lipid raft formation
- Translocation
- Statin
  - 15–500 mg/l
- 4 mg/l
- 40–62 mg/l/2–4 x MIC
- 0.2–20 mg/l
- 0.25–50 mg/kg/day
- 0.1–20 mg/l
- Intracellular growth
- Rho GTPase
- Cholesterol

C. In vivo
- Bacterial load
- Dissemination
- Bacterial clearance

Pleiotrophic Effects. Statins Have No Benefit For CAC = 0. Independent of Cholesterol Level. (Mitchell, JACC, 2018)

Incidence of MACE
Calcium Score = 0

<table>
<thead>
<tr>
<th>Statin</th>
<th>No Statin</th>
</tr>
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<tbody>
<tr>
<td>5,618</td>
<td>5,355</td>
</tr>
<tr>
<td>3,742</td>
<td>3,632</td>
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<tr>
<td>4,872</td>
<td>3,258</td>
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<tr>
<td>2,973</td>
<td>1,978</td>
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<tr>
<td>600</td>
<td>318</td>
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</tbody>
</table>
Cumulative Incidence MACE With and W/O Statin


Statin vs. No Statin
aSHR 0.32, 95% CI 0.21-0.48
p < 0.0001

CAC 100-400

Cumulative Incidence MACE

CUMULATIVE INCIDENCE

0.20 -

0.15 -

0.10 -

0.05 -

0.00 -

0.00 3 6 9 12

Year

Statin

No Statin

CAC 101-400

MACE

Cumulative Incidence
Statin Drugs - Summary

- Power of Zero = No Benefit for Statin Regardless of Cholesterol Level.
- The Higher the Calcium Score, the Greater the Benefit, Due to Pleiotrophic Effects, Regardless of Cholesterol Level.
- If on a Statin and CAC Increases >15% - Statin Treatment Failing, High Risk for MI.

Interventions for Calcium Score
Advantage
Integrative Medicine
Mainstream Cardiology Clings to Cholesterol Hypothesis with Statin Monotherapy.

Integrative Medicine Champions Calcium Score to Establish Risk and Monitor Therapy, Apply Integrative Therapies.
Leaky Gut/LPS/Endotoxemia

- Block
  - Activation of NF-Kb
    - Block
      - Infected Biofilm
        - Block
          - Calcified Plaque

Series of Steps

- Progression?
  - Active Disease
    - Non-Progression
      - In-Active Disease
## What Works for Preventing Progression of CAC

<table>
<thead>
<tr>
<th>What Works</th>
<th>Preventing Progression of CAC</th>
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<tbody>
<tr>
<td>Vitamin C</td>
<td>(Linus Pauling)</td>
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<tr>
<td>Vitamin K2</td>
<td>- MK7</td>
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<tr>
<td>Magnesium</td>
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<td>Vitamin D3</td>
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<td>Tocotrienol Vit E</td>
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<tr>
<td>Aged Garlic</td>
<td>- Allicin</td>
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<td>Essential Phospholipid</td>
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<tr>
<td>Botanicals</td>
<td>for NFKB</td>
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<tr>
<td>Address</td>
<td>Leaky Gut</td>
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<tr>
<td>Eliminate</td>
<td>Wheat</td>
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<td>Optimize</td>
<td>Hormones</td>
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<td>Control</td>
<td>Blood Sugar</td>
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<td>Fibrinolytic</td>
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<td>EDTA</td>
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<td>MTHFR ?</td>
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<td>Homocysteine?</td>
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<td>Lipoprotein(a) ?</td>
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<tr>
<td>Statins</td>
<td>Accelerate or Retard</td>
</tr>
<tr>
<td>Vascular</td>
<td>Calcification ?</td>
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</tbody>
</table>

Heart Book by Jeffrey Dach, MD 2018 Medical Muse Press.
Linus Pauling: heart disease is a manifestation of chronic scurvy.

Stop America's #1 Killer T Levy 2006 CAD is reversible scurvy.


Aged Garlic for Calcium Score

- Reduces Progression of Calcium Score 60-70%
  Compared to Controls.


Aged Garlic
Genetically Modified Mice

Daily Garlic (Allicin) Reduced Plaque Area 70% in ApoE-Deficient Mice, 60% in LDL Receptor Knockout Mice.

No Effect on Lipid Levels.

Human: Reduces Soft Plaque (Matsumoto)


Allicin Reduces Plaque in Apo-E Mice
Garlic (Allicin) Effective For Pseudomonas Biofilm

- Garlic is Anti-Microbial.
- Garlic Effective Against Pseudomonas Biofilm.
- Inhibits Quorum Sensing and Virulence. (66-67)

Botanicals Inhibit NF-KB

- Garlic - Allicin (Keiss, 2003)(Wang, 2016)
- Berberine (Closes Tight Junctions), (Jia L, 2012)(Mo, 2014)
- Boswellia, (Cuaz-Pérolin, 2008)
- Chinese Skullcap Oroxylin (Anti-Viral), (Yao, 2014) (Tseng, 2012)
- Curcumin, (Jobin, 1999)
- Resveratrol, Pterostilbene (Yao, 2018)
- Phosphatidylcholine (EPC) (Cheng, 2018)
References: Botanicals Inhibit NF-KB

Leaky Gut and Coronary Artery Disease

- Leaky Gut Causes Metabolic Endotoxemia.
- Activated NFκB, Elevated Cytokines IL-6, TNF-A.
- Polymicrobial Biofilm.
- Vascular Calcification - Calcium Score
- Linked to Metabolic Syndrome, AODM, Obesity, Atherosclerosis, Neurological Dis., Parkinson’s


Leaky Gut Interventions

• **Remove**
  - NSAIDS
  - PPI’s
  - Alcohol
  - Wheat Gluten
  - Reactive Foods
  - Glyphosate
  - GMO Food
  - Pesticides

• **Add**
  - Berberine
  - Probiotics
  - Digestive Enzymes
  - Fiber
  - Glutamine
  - Colostrum
  - Zinc (Resnick, 2010)

Hormonal Optimization for Calcium Score?

- **Thyroid** (Barnes, Asvold-Hunt, 2008; Zhu, 2014)
- **Estrogen** (Budoff, 2005) (22% vs 9%)
- **Testosterone** (Muraleedharan, 2013; Haider, 2016)

References: see next slide
Future Research
Add Integrative Arm Raggi 2004

Identify Progressors at 2 yrs. Add Calcium Score Protocol, Third Arm Blue Line.

495 on Statins
41 pts, Acute MI

<15%

>15%

p<0.0001
Case Report
Reduction in Calcium Score

57 y/o Male Loading Dock Worker
CAC 1,212 Progressed to 1,650 Over Previous 7 Months –
61% Annual Increase.

Started on CAC Protocol
One Year Later: Calcium Score was 1,543
6.5% Annual Decrease.
Thank You – Any Questions?

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