

A Message from your Heart; Answers for Cardiovascular Disease International College of Integrative Medicine March 6-10, 2019 Philadelphia.

## Calcium Score Progression the Paradigm Shift in Cardiology



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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

Allam, Adel H., et al. "Atherosclerosis in ancient Egyptian mummies: the Horus study." JACC: Cardiovascular Imaging 4.4 (2011): 315-327. Thomas, Gregory S., et al. "Why did ancient people have atherosclerosis?: from autopsies to computed tomography to potential causes." Global heart 9.2 (2014):

# 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)

Mitchell, Joshua D., et al. "Impact of statins on cardiovascular outcomes following coronary artery calcium scoring." Journal of the American College of Cardiology 72.25 (2018): 3233-3242.

## Imaging Atherosclerotic Disease



Figure 2 Meinel, Felix G., et al. "Diagnostic yield and accuracy of coronary CT angiography after abnormal nuclear myocardial perfusion imaging." Scientific reports 8.1 (2018): 9228.

#### Imaging with SPECT Perfusion, CT-Angio and Cath Angiography



## CAT Scan Coronary Artery Calcification



## Calcified LAD.

Quantify Calcium

Agatson Score

Orakzai, S. H., et al. "Measurement of coronary artery calcification by electron beam computerized tomography in persons with chronic spinal cord injury: evidence for increased atherosclerotic burden." Spinal Cord 45.12 (2007): 775.



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#### **CAC Progression Paradigm Shift - 2004**



Raggi, Paolo, Tracy Q. Callister, and Leslee J. Shaw. "Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy." *Arteriosclerosis, thrombosis, and vascular biology* 24.7 (2004): 1272-1277.

## The Big Picture - Summary Slide

- 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.

Brown, Michael S., and Joseph L. Goldstein. "How LDL receptors influence cholesterol and atherosclerosis." Scientific American 251.5 (1984): 58-69.



"The More X There is in the Blood, the More Rapidly Atherosclerosis Develops."

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

Brown, Michael S., and Joseph L. Goldstein. "How LDL receptors influence cholesterol and atherosclerosis." Scientific American 251.5 (1984): 58-69.

## **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)
- 7) Women- Lipid Lowering No Benefit. (Judith Walsh, 2004)

#### **References Cholesterol Theory Falsified**

- Hecht, Harvey S., et al. "Relation of coronary artery calcium by electron beam tomography to serum lipoprotein levels." AJ Cardiology 87.4 (2001): 406-412.
- Raggi, Paolo et al. "Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy." Arteriosclerosis, thrombosis, and vascular biology 24.7 (2004): 1272-1277.
- Neil, Andrew, et al. "Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study." European heart journal 29.21 (2008): 2625-2633
- Horwich, Tamara B., and Gregg C. Fonarow. "Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS." Seminars in dialysis. Vol. 20. No. 6. 2007.
- Lincoff, A. Michael, et al. "Evacetrapib and cardiovascular outcomes in highrisk vascular disease." New Eng J Medicine 376.20 (2017): 1933–1942.
- 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
- Walsh, Judith ME, and Michael Pignone. "Drug treatment of hyperlipidemia in women." Jama 291.18 (2004): 2243-2252.

Cholesterol Does **NOT** Cause Vascular Calcification

- 2001 Calcium Score Study (EBT)
- 930 Asymptomatic Pts. Not On Statins.
- Non-Correlation

This Disproves the Hypothesis that Cholesterol Causes Vascular Calcification.

Hecht, Harvey S., et al. "Relation of coronary artery calcium by electron beam tomography to serum lipoprotein levels." American J Cardiology, 87.4 (2001): 406-412.

#### **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)

Landé, K. E., and W. M. Sperry. "Human atherosclerosis in relation to the cholesterol content of the blood serum." Arch. Pathol. 22 (1936): 301-312. Mathur, K. S., et al. "Serum cholesterol and atherosclerosis in man." Circulation 23.6 (1961): 847-852.

## 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.

Lincoff, A. Michael, et al. "Evacetrapib and cardiovascular outcomes in high-risk vascular disease." New England Journal of Medicine 376.20 (2017): 1933

## Falsifying the Cholesterol Theory Zero CAC – Lifelong Cholesterol 580



Johnson, Kipp W., Joel T. Dudley, and Jason R. Bobe. "A 72-Y/O Untreated Familial Hypercholesterolemia but no Coronary Artery Calcification: Case Report." Cureus 10.4 (2018). Miname M,"Coronary Artery Calcium and Cardiovascular Events in Patients With Familial Hypercholesterolemia Receiving Standard Lipid-Lowering Therapy" JACC: Cardiovascular Imaging. Zero Score = Zero Future Events. Avoid Statins.

# The Endotoxin-Lipoprotein Hypothesis

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

Sandek A., Utchill S, Rauchhaus M. The endotoxin-lipoprotein hypothesis-an update. Arch Med Sci. 2007;3(4A):S81. The endotoxin lipoprotein hypothesis Anja Sandek 2007

# Atherosclerotic Plaque What is it?

# Activated NF-Kb PlaqueCalcification And More

#### Atherosclerotic Plaque – Activated NF-KB



Brand, et al. "Activated transcription factor nuclear factor-kappa B is present in atherosclerotic lesion." J Clin Invest 1996.

#### **Activated Nuclear Factor Kappa B**

Lanter, B. B., and D. G. Davies. "Propionibacterium acnes Recovered from Atherosclerotic Human Carotid Arteries Undergoes Biofilm Dispersion and Releases Lipolytic and Proteolytic Enzymes in Response to Norepinephrine Challenge In Vitro." Infection and immunity 83.10 (2015): 3960-3971.

#### 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 TNFalpha, which drives vascular calcification.

Proposed mechanisms for anti-inflammatory in LPSinduced macrophages.

 Zhang "Molecular mechanisms of NF-κB activation induced by bacterial lipopolysaccharide through Toll-like receptors." J of Endotoxin Res 6.6 (2000): 453-457.

#### **Arterial Calcification Stains Green**



Doherty, Terence "Calcification in atherosclerosis: bone biology and chronic inflammation." PNAS (2003) 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



Nakahara, Takehiro, et al. "Coronary artery calcification: from mechanism to molecular imaging." JACC: Cardiovascular Imaging 10.5 (2017): 582-593.

#### **Evolution of Calcified Atheroma Plaque**



Nakahara, Takehiro, et al. "Coronary artery calcification: from mechanism to molecular imaging." JACC: Cardiovascular Imaging 10.5 (2017): 582-593.



Kozarov, Emil, Teresa Padro, and Lina Badimon. "View of statins as antimicrobials in cardiovascular risk modification." Cardiovascular research 102.3 (2014): 362-374.

## Vascular Calcification – What is It?

- "Vascular Calcification is a Clinical Marker for Atherosclerosis".
- "May Represent a Special Example of Soft Tissue Calcification Surrounding Chronic Inflammatory Foci." (Abedin, 2004)
- Chronic Inflammatory Focus = Infection.

Abedin, Moeen, Yin Tintut, and Linda L. Demer. "Vascular calcification: Mechanisms and clinical ramifications." Arteriosclerosis, Thrombosis, and Vascular Biology 24.7 (2004): 1161–1170..

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

## Cholesterol or Infection? TB Pericarditis



Goel, Pravin K., and Nagaraja Moorthy. "Tubercular chronic calcific constrictive pericarditis." (2011). Heart Views. 2011 Jan-Mar; 12(1): 40–41.

### Cysticercosis



Banu, A., and N. Veena. "A rare case of disseminated cysticercosis: Case report and literature review." Indian journal of medical microbiology 29.2 (2011): 180.

## **Echinacoccus Cyst Liver**



Neto, Nelson. "Abdominal Hydatidosis–Imaging Features." European Congress of Radiology 2013, 2013.

## What is the Evidence for Infection in Atherosclerotic Plaque ?

#### Atherosclerotic Plaque is Poly-Microbial Biofilm

Patient 26

Patient 27



Ribosome **RNA** Ludwig, W. "Bacterial phylogeny based on 16S and 23S rRNA sequence analysis." **FEMS** Microbiology Rev 1994.

**Lanter, B**. B., and D. G. Davies. "Propionibacterium acnes Recovered from Atherosclerotic Human Carotid Arteries Undergoes Biofilm Dispersion and Releases Lipolytic and Proteolytic Enzymes in Response to Norepinephrine Challenge In Vitro." Infection and immunity 83.10 (2015): 3960-3971.

## Plaque is Infected Biofilm

- 16s Ribosome RNA, FISH Technique
- Atherosclerotic Plaque Samples
- Atherosclerotic Plaque is Infected Biofilm Colonized by Bacterial, Fungal and Protozoal Organisms.

**Lanter, Bernard** et al "Bacteria present in carotid arterial plaques are found as biofilm deposits " MBio 5.3 (2014): e01206-14.

Lanter, B. B., and D. G. Davies. "Propionibacterium acnes Recovered from Atherosclerotic Human Carotid Arteries Undergoes Biofilm Dispersion." Infection and immunity 83.10 (2015): 3960-3971.

Ott, Stephan J., et al. "Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease." Circulation 113.7 (2006): 929-937.

## Plaque is Infected Biofilm

### Cultivation of Micro-Organisms from Diseased Tissue has been Demonstrated

Kozarov, Emil. "Bacterial invasion of vascular cell types: vascular infectology and atherogenesis." Future cardiology 8.1 (2012): 123-138.

## Atherosclerotic Plaque as Polymicrobial Infected Biofilm

- Carnevale, Roberto, et al. "Localization of lipopolysaccharide from Escherichia Coli into human atherosclerotic plaque." Scientific reports 8.1 (2018): 3598.
- Mawhorter SD, Lauer MA. Is atherosclerosis an infectious disease? Cleve Clin J Med. 2001;68(5):449-58.
- Kuo CC, Shor A, Campbell LA, et al. Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. J Infect Dis. 1993;167(4):841-9.
- Fry SE, et al Putative biofilm-forming organisms in the human vasculature: expanded case reports and review of the literature. Phlebological Review 2014; 22(1): 24–37.
- Lanter BB, et al. Bacteria present in carotid arterial plaques are found as biofilm deposits which may contribute to enhanced risk of plaque rupture. MBio. 2014;5(3):
- Ott SJ, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. Circulation. 2006;113(7):929-37.
- Ott SJ, et al. Fungal rDNA signatures in coronary atherosclerotic plaques. Environ Microbiol. 2007;9(12):3035-45.
- Koren O, at al. Human oral, gut, and plaque microbiota in patients with atherosclerosis.
  Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4592-8.
- Chakravorty, S et al. "Detailed analysis of 16S ribosomal RNA gene segments for diagnosis of pathogenic bacteria." Journal of microbiological methods 69.2 (2007): 330-339.
#### Interventions for Infected Biofilm

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

Harjai, K "Garlic blocks quorum sensing and attenuates the virulence of Pseudomonas aeruginosa." FEMS immunology and medical microbiology 58.2 (2010): 161. Liu, Zhenqiu, et al. "In vitro and in vivo activity of EDTA and antibacterial agents against the biofilm of mucoid Pseudomonas aeruginosa." Infection 45.1 (2017): 23-31. Molobela "Protease and amylase enzymes for removal and degradation of Pseudomonas fluorescens biofilm." African J of Microbiology Resh 4.14 (2010): 1515. Delgado-Roche "Ozone oxidative preconditioning prevents atherosclerosis development in New Zealand white rabbits." J Cardiovasc Pharm 2013

# Bacterially-Derived Signals Drive Cardio-Metabolic Diseases.



#### LPS from Leaky Gut

#### **Atherosclerotic CVD**

**Brown, er al**. "The Gut Microbial Endocrine Organ: Bacterially-Derived Signals Driving Cardiometabolic Diseases." Ann Rev Med 66 (2015): 343.

### 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

Li, Chuanwei, et al. "Zonulin regulates intestinal permeability and facilitates enteric bacteria permeation in coronary artery disease." Scientific reports 6 (2016): 29142. Lehr, Hans-Anton, et al. "Endotoxin accelerates atherosclerosis in rabbits on hypercholesterolemic diet." Circulation 104.8 (2001): 914-920. Cuaz-Pérolin, Clarisse, et al. "Antiinflammatory and antiatherogenic effects of the NF-κB inhibitor boswellic acid in LPS-challenged ApoE-/- mice." Arteriosclerosis, thrombosis, and vascular biology 28.2 (2008): 272-277.

#### 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)

**Chukkapalli,** Sasanka S., et al. "Polymicrobial oral infection with four periodontal bacteria orchestrates a distinct inflammatory response and atherosclerosis in ApoEnull mice." PLoS One 10.11 (2015): e0143291. Chukkapalli, Sasanka S., et al. "Sequential colonization of periodontal pathogens in induction of periodontal disease and atherosclerosis in LDLRnull mice." Pathogens and disease 75.1 (2017). Chhibber-Goel, Jyoti, et al. "Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients." NPJ biofilms and microbiomes 2.1 (2016): 7. 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.

**Chhibber-Goel**, Jyoti, et al. "Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients." NPJ biofilms and microbiomes 2.1 (2016): 7.

# 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.

Samanta, Anweshan, et al. "SUBTOTAL LEFT MAIN DISEASE IN PATIENT WITH ZERO CALCIUM SCORE: IS IT POSSIBLE?." Journal of the American College of Cardiology 71.11 Supplement (2018): A2197.

# Baseline Calcium Score Powerful Predictor of Impaired Survival



Al-Mallah, Mouaz H., et al. "Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease?" European Heart Journal 15.3 (2013): 267-274.

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 Ml's over 6 years.
- Mean LDL Did Not Differ !!!
- 118 vs. 122 mg/dL, (MI versus Non-MI)

Raggi, Paolo, Tracy Q. Callister, and Leslee J. Shaw. "Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy." *Arteriosclerosis, thrombosis, and vascular biology* 24.7 (2004): 1272-1277.

#### **CAC Progression Paradigm Shift - 2004**



Raggi, Paolo, Tracy Q. Callister, and Leslee J. Shaw. "Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy." *Arteriosclerosis, thrombosis, and vascular biology* 24.7 (2004): 1272-1277.

#### **CAC Progression Paradigm Shift - 2004**



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

# Pleotropic Effects Overwhelmed by Severe Endotoxemia.

#### **Annual Calcium Score Progression**



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

#### **Calcium Score in Diabetics**



Raggi et al. (22) Prognostic value of coronary artery calcium screening in subjects with and without diabetes. Journal of the American College of Cardiology 2004;43(9):1663-1669.

Progression of CAC What Does it Mean?

- Progression of Calcification Means Active Disease in the Arterial Wall. (Infection and Inflammation)
- 17-Fold Increased Risk fof 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.

Dykun, Iryna, et al. "Statin medication enhances progression of coronary artery calcification: the Heinz Nixdorf Recall Study." Journal of the American College of Cardiology 68.19 (2016): 2123-2125 Statin Benefits Due Entirely to Pleotrophic Effects

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

Curtis, Michael, et al. "Effect of Dose and Timing of Preoperative Statins on Mortality After Coronary Artery Bypass Surgery." The Annals of Thoracic Surgery (2017). Barakat, Amr F., et al. "Perioperative statin therapy for patients undergoing coronary artery bypass grafting." The Annals of thoracic surgery 101.2 (2016): 818-825. Hennessy, Emma, et al. "Is there potential for repurposing statins as novel antimicrobials?." Antimicrobial agents and chemotherapy 60.9 (2016): 5111-5121.

# Statins Pleotrophic 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)

Patel, Tushar R., and Siobhan A. Corbett. "Simvastatin suppresses LPS-induced Akt phosphorylation in the human monocyte cell line THP-1." Journal of Surgical Research 116.1 (2004): 116-120. Devaraj et al "Direct demonstration of an antiinflammatory effect of simvastatin in

Devaraj et al"Direct demonstration of an antiinflammatory effect of simvastatin in subjects with the metabolic syndrome." J Clin Endo & Metab 91.11 (2006): 4489-4496. Hölschermann, Hans, et al. "Statins prevent NF-κB transactivation independently of the IKK-pathway in human endothelial cells." Atherosclerosis 185.2 (2006): 240-245.

#### Repurposing Statins as Novel Antimicrobials?



Hennessy, Emma, et al. "Is there potential for repurposing statins as novel antimicrobials?." Antimicrobial agents and chemotherapy 60.9 (2016): 5111-5121.

# **POWER of Zero**



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

#### Cumulative Incidence MACE With and W/O Statin



Mitchell, Joshua "Impact of statins on cardiovascular outcomes following coronary artery calcium scoring." J Amer College of Cardiology 72.25 (2018): 3233-3242.

#### 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 Pleotrophic Effects, Regardless of Cholesterol Level.
- If on a Statin and CAC Increases >15% -Statin Treatment Failing, High Risk for MI.

Oesterle, A., U. Laufs, and J. K. Liao. "Pleiotropic Effects of Statins on the Cardiovascular System." Circulation research 120.1 (2017): 229-243.

# Interventions for Calcium Score Advantage Integrative Medicine



### **Advantge 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.



#### What Works for Preventing Progression of CAC

- Vitamin C (Linus Pauling)
- Vitamin K2 MK7
- Magnesium
- Vitamin D3
- Tocotrienol Vit E
- Aged Garlic Allicin
- Essential Phospholipid
- Botanicals for NFKB
- Address Leaky Gut
- Eliminate Wheat

- Optimize Hormones
- Control Blood Sugar
- Fibrinolytic Enzymes
- Ozone
- EDTA
- MTHFR ?
- Homocysteine?
- Lipoprotein(a) ?
- Statins Accelerate or Retard Vascular Calcification ?

Heart Book by Jeffrey Dach , MD 2018 Medical Muse Press.

#### References: What Works for CAC

- Linus Pauling: heart disease is a manifestation of chronic scurvy.
- Stop America's #1 Killer T Levy 2006 CAD is reversible scurvy.
- Maeda, Nobuyo, et al. "Aortic wall damage in mice unable to synthesize ascorbic acid." Proc Nat Acad of Sciences (2000): 841
- Shea et al. "Vit K supplementation and progression of coronary artery calcium in older men and women." Am j clin nut (2009)
- Braake, Anique D., et al. "Magnesium prevents vascular calcification in vitro by inhibition of hydroxyapatite crystal formation." Scientific reports 8.1 (2018):
- Equils, O., et al. "Vitamin D3 inhibits LPS -induced immune activation in human endothelial cells." Clin Exp Immun (2006)
- Ramanathan, et al. "Tocotrienol is a cardioprotective agent against ageing-associated cardiovascular disease ." Nut & metab (2018)
- Cheng, et al. "Phosphatidylcholine regulates NF-κB activation in attenuation of LPS-induced inflammation: in vitro study." Animal Cells Systems 22.1 (2018):

# Aged Garlic for Calcium Score



Budoff M. Aged garlic extract retards progression of coronary artery calcification. J Nutr. 2006;136(3 Suppl):741S-744S.

Budoff MJ, Ahmadi N, Gul KM, et al. Aged garlic extract supplemented with B vitamins, folic acid and L-arginine retards the progression of subclinical atherosclerosis: a randomized clinical trial. Prev Med. 2009;49(2-3):101-7.

Zeb I, Ahmadi N, Nasir K, et al. Aged garlic extract and coenzyme Q10 have favorable effect on inflammatory markers and coronary atherosclerosis progression: A randomized clinical trial. J Cardiovasc Dis Res. 2012;3(3):185-90.

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)

Gonen A, Harats D, Rabinkov A, et al. The antiatherogenic effect of allicin: possible mode of action. Pathobiology. 2005;72(6):325-34. Tel Hashomer
Matsumoto, Suguru, et al. "Aged Garlic Extract Reduces Low Attenuation Plaque in Coronary Arteries of Patients with Metabolic Syndrome in a Prospective Randomized Double-Blind Study–3." The Journal of nutrition 146.2 (2016): 427S-432S.

# Allicin Reduces Plaque in Apo-E Mice

В

#### Placebo

#### Allicin (Garlic)

# Garlic (Allicin) Effective For Pseudomonas Biofilm



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

Bjarnsholt T, Givskov M. The role of quorum sensing in the pathogenicity of the cunning aggressor Pseudomonas aeruginosa. Anal Bioanal Chem. 2007;387(2):409-14. Harjai K, Kumar R, Singh S. Garlic blocks quorum sensing and attenuates the virulence of Pseudomonas aeruginosa. FEMS Immunol Med Microbiol. 2010;58(2):161-8. Lihua L, Jianhuit W, Jialini Y, Yayin L, Guanxin L. Effects of allicin on the formation of Pseudomonas aeruginosa biofinm and the production of quorum-sensing controlled virulence factors. Pol J Microbiol. 2013;62(3):243-51.

#### **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

- Jia L, Liu J, Song Z, et al. Berberine suppresses inflammatory response by inhibiting NFK-B and MAP-K signaling pathways. J Pharm 2012;64:1510–1521.
- Mo, C., et al. "anti-inflammatory effect of berberine in LPS-stimulated macrophages and endotoxin-shocked mice." Antioxidants & redox signaling 20.4 (2014): 574.
- Cuaz-Pérolin, Clarisse, et al. "Antiinflammatory and antiatherogenic effects of NF-κB inhibitor boswellic acid in LPS-challenged mice." Arterio, thromb vasc bio 28.2 (2008):
- Yao, Jing, et al. "Oroxylin A prevents inflammation-related tumor by inhibiting NF-κB signaling." Molecular carcinogenesis 53.2 (2014): 145–158.
- Tseng, Tzu-Ling, et al. "Oroxylin-A rescues LPS-induced acute lung injury via regulation of NF-κB signaling pathway in rodents." PLoS One 7.10 (2012): e47403.
- Jobin, Christian, et al. "Curcumin blocks cytokine-mediated NF-κB activation and proinflammatory gene expression." J of Immunology 163.6 (1999): 3474-3483.
- Keiss, Hans-Peter, et al. "Garlic (Allium sativum L.) modulates cytokine expression in LPSactivated human blood thereby inhibiting NF-κB " J of nutrition (2003): 2171
- Wang, et al. "Allicin reduces IL-1β-induced inflam cytokines via attenuating the NF-κB and MMP3 activation in chondrocytes." Int J Clin Exp Path 9.10 (2016): 10320-10326.
- Yao, Yun, et al. "Pterostilbene and resveratrol Inhibited LPS-Induced Inflammatory Response in RAW264. 7 Macrophages." Molecules 23.5 (2018): 1148.
- de Sá Coutinho, Diego, et al. "Anti-inflammatory effects of resveratrol: Mechanistic insights." International journal of molecular sciences 19.6 (2018): 1812.
- Cheng, Meijuan, et al. "Phosphatidylcholine regulates NF-κB activation in attenuation of LPS-induced inflammation: in vitro study." Animal Cells Systems 22.1 (2018): 7-14.

# Leaky Gut and Coronary Artery Disease

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

Brown, J. Mark et al. "The Gut Microbial Endocrine Organ: Bacterially-Derived Signals Driving Cardiometabolic Diseases." Annual review of medicine 66 (2015): 343.

Rice, James B., et al. "Low-level endotoxin induces potent inflammatory activation of human blood vessels inhibition by statins." Arteriosclerosis, thrombosis, and vascular biology 23.9 (2003): 1576-1582.

#### 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)

**Resnick C.** Nutritional protocol for the treatment of intestinal permeability defects and related conditions. NMJ, 2010;2(3), 14-23.

Hormonal Optimization for Calcium Score?

Strain (Barnes, Asvold-Hunt, 2008, Zhu, 2014)

Estrogen (Budoff, 2005) (22% vs 9%)

Testosterone (Muraleedharan,2013 Haider,2016)

References: see next slide
### Hormones: References

Barnes, Broda Otto, Solved: the riddle of heart attacks. Robinson Press, 1976. Åsvold, Bjørn O., et al. "Thyrotropin levels and risk of fatal coronary heart disease: the HUNT study." Archives of internal medicine 168.8 (2008): 855-860. Zhu, Lijie, et al. "Relationship of serum free T3 with the coronary artery calcification and major adverse cardiac events in patients with suspected coronary artery disease."  $(201\overline{4})$ Manson, JoAnn E., et al. "Estrogen therapy and coronary-artery calcification." New England Journal of Medicine 356.25 (2007): 2591-2602. Budoff, Matthew J., et al. "Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography." Journal of women's health 14.5 (2005): 410-417 Muraleedharan, Vakkat, et al. "Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes." European Journal of Endocrinology 169.6 (2013): 725-733. Haider, Ahmad, et al. "Men with testosterone deficiency and a history of cardiovascular diseases benefit from long-term testosterone therapy: observational, real-life data from a registry study." Vascular health and risk management 12 (2016): 251

## **Future Research** Add Integrative Arm Raggi 2004



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

### 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.

Heart Book by Jeffrey Dach MD 2018 Medical Muse Press

### White Cliffs of Dover Microbial Calcification



## HEART BOOK

# Thank You – Any Questions?

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