ASCVD RISK REDUCTION THERAPY: BEYOND STATINS

Age at Death of Mummies With and Without Atherosclerosis

Princess
OBJECTIVES

1. Recognize the interrelationship of insulin resistance to atherosclerosis
2. Importance of genetic influence on hypertension
3. Increasing risk of atherosclerosis by duration of high lipids
4. Amplification of CV risk with hypertension and lipids
5. New guidelines
   a. BP
   b. Lipids
Calcifications in the left and right coronary arteries (arrows) in the mummy.

Extensive calcifications along the course of the superficial femoral arteries in the mummy of a man who lived during the 18th Dynasty.
OVERVIEW: COMPLEXITY OF THE HIGH RISK CARDIO-METABOLIC PATIENT

Environmental epigenetic effects
- Increasing insulin resistance
- Cellular dysfunction
- Endothelial dysfunction

Common risk factors recognized
- Treatment of numbers: BP <120, LDL <50, hsCRP <0.1 etc
- Drugs: primary treatment
  - Rarely lifestyle followed long term

↑ CV risk
For > 10yrs

Human awakening as vascular events occur
(Life span shortens 7-13 years)
YEARLY MORTALITY (DEATH) IN MEDICALLY TREATED PATIENTS BY CORONARY ANGIOGRAM

Percent mortality per year

- 1 vessel dx: 1.4
- 2 vessel dx: 2.4
- 3 vessel dx: 4.2
- 3VDx + prox 95% LAD: 8.2

J Am Coll Cardiol. 1996;27:964–1047

Adapted from al Patel et al
WHAT PERCENTAGE YOUNG ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE Atherosclerosis?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%

Answer 5 > 70%
High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults
Evidence From Intravascular Ultrasound

E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

Background—Most of our knowledge about atherosclerosis at young ages is derived from necropsy studies, which have inherent limitations. Detailed, in vivo data on atherosclerosis in young individuals are limited. Intravascular ultrasonography provides a unique opportunity for in vivo characterization of early atherosclerosis in a clinically relevant context.

Methods and Results—Intravascular ultrasound was performed in 262 heart transplant recipients 30.9±13.2 days after transplantation to investigate coronary arteries in young asymptomatic subjects. The donor population consisted of 146 men and 116 women (mean age of 33.4±13.2 years). Extensive imaging of all possible (including distal) coronary segments was performed. Sites with the greatest and least intimal thickness in each CASS segment were measured in multiple coronary arteries. Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic. A total of 2044 sites within 1477 segments in 574 coronary arteries (2.2 arteries per person) were analyzed. An atherosclerotic lesion was present in 136 patients, or 51.9%. The prevalence of atherosclerosis varied from 17% in individuals <20 years old to 85% in subjects ≥50 years old. In subjects with atherosclerosis, intimal thickness and area stenosis averaged 1.08±0.48 mm and 32.7±15.9%, respectively. For all age groups, the average intimal thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in men and 51.7% in women).

Conclusions—This study demonstrates that coronary atherosclerosis begins at a young age and that lesions are present in 1 of 6 teenagers. These findings suggest the need for intensive efforts at coronary disease prevention in young adults.

(Circulation. 2001;103:2705-2710.)
IMPORTANCE OF GENETIC FACTORS WHEN PICKING YOUR PARENTS

Selected risk factor variables in offspring ages 18 to 31 years by parental history of disease, race, and sex

Bogalusa Heart Study

Circ 1995; 91: 365-371
FRAMINGHAM OFFSPRING STUDY

“PICKING YOUR PARENTS”

Both parents w/o CVD <55 man (<65 women) (Good)

N=2302

8 yr CVD Event Rate Per 1000

1>Premature CADx

1>Good Parents

<40 HDL | No DM | Smoker | BMI 25-29 | TC 200-239
---|---|---|---|---
Good Parents | 42 | 30 | 57 | 37 | 23
1>CADx | 125 | 90 | 143 | 110 | 119

p=all significant

JAMA May 12, 2004;291:2204-2211
LANDMARK PAPER: BOGALUSA HEART STUDY

- Autopsies on 204 young persons 2 to 39 years...TRAUMA

N Engl J Med
1998;338:1650-6
Cardiovascular risk factors increase the amount of disease

AUTOPSY RESULTS BY AGE 21-29

85% coronary arteries have fatty streaks

50-69% have coronary atheroma

Time Genetics Metabolism Inflammation

YEARS OF HIGH LIPID INCREASED CV EVENTS

- Framingham Offspring Cohort data - identify adults without incident cardiovascular disease to 55 years of age (n=1478)
- Moderate hyperlipidemia (non-high-density lipoprotein cholesterol ≥160 mg/dL (35-50 y/o)
- Median 15-year follow-up
- CHD rates were significantly elevated among adults with prolonged hyperlipidemia exposure by 55 years of age

Circulation 2015;131:451-458
MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP

N=316 099

Arch Intern Med. 1992;152:56-64
TARGETING INFLAMMATION

High inflammatory state

Significant increase in CV events
Cholesterol Crystals → Neutrophil Extracellular Traps → Athero-prone Flow → Hypoxia (O₂)

Pro-IL-1β → Caspase-1 → Active IL-1β → NLRP3 Inflammasome

↑ INOS, Endothelin-1, Chemokines, Cytokines, Adhesion Molecules, Macrophage Activation, Smooth Muscle Proliferation

↑ Vascular Inflammation, Endothelial Dysfunction, Atherosclerosis

IL-1β → IL-6 → PAI-1 → Fibrinogen → Liver → CRP

Canakinumab


Vascular Risk hsCRP (mg/L)
High .................. >3
Intermediate .......... 1-3
Low .................. <1
Canakinumab Dose (mg/month)

- Median Reduction

Fibrinogen

Interleukin-6

C-reactive Protein

Ridker PM, et al; Circulation 2012; 126:2739-2748
CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP (≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

Randomized
Canakinumab 50 mg
SC q 3 months

Randomized
Canakinumab 150 mg
SC q 3 months

Randomized
Canakinumab 300 mg
SC q 3 months*

Randomized
Placebo
SC q 3 months

Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)
<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>4.5</td>
<td>4.1</td>
<td>3.9</td>
<td>3.9</td>
<td>0.020</td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>0.93</td>
<td>0.85</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>0.80-1.07</td>
<td>0.74-0.98</td>
<td>0.75-0.99</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>(referent)</td>
<td>0.30</td>
<td>0.021*</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>5.1</td>
<td>4.6</td>
<td>4.3</td>
<td>4.3</td>
<td>0.003</td>
</tr>
<tr>
<td>HR</td>
<td>1.00</td>
<td>0.90</td>
<td>0.83</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>0.78-1.03</td>
<td>0.73-0.95</td>
<td>0.72-0.94</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>(referent)</td>
<td>0.11</td>
<td>0.005*</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>
CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.

HR 0.85
95% CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>12.0</td>
<td>11.4</td>
<td>11.7</td>
<td>12.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24</td>
<td>0.30</td>
<td>0.37</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.86</td>
<td>3.03</td>
<td>3.13</td>
<td>3.25</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>0.18</td>
<td>0.31</td>
<td>0.28</td>
<td>0.34</td>
<td>0.09/0.02*</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0.23</td>
<td>0.27</td>
<td>0.28</td>
<td>0.30</td>
<td>0.49</td>
</tr>
<tr>
<td>Any Malignancy</td>
<td>1.88</td>
<td>1.85</td>
<td>1.69</td>
<td>1.72</td>
<td>0.31</td>
</tr>
<tr>
<td>Fatal Malignancy</td>
<td>0.64</td>
<td>0.55</td>
<td>0.50</td>
<td>0.31</td>
<td>0.0007</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32</td>
<td>2.15</td>
<td>2.17</td>
<td>2.47</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67</td>
<td>1.21</td>
<td>1.12</td>
<td>1.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80</td>
<td>0.43</td>
<td>0.35</td>
<td>0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT &gt; 3x normal</td>
<td>1.4</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Bilirubin &gt; 2x normal</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Translational biology
RISK OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH SELECTED CV RISK FACTORS - 80% FROM 4 MAJOR FACTORS

Adapted from Yusuf et al.
Lancet 2004; 364: 937–52
INCREASED PROTEIN EXPRESSION OF SGLT2 IN TYPE 2 DM

- Insulin resistance / T2DM
- Hyperglycemia increases the filtered load of glucose at the glomerulus, and glomerular hyperfiltration itself is also associated with diabetes
- Glucose transporters in human renal proximal tubular cells in T2DM

Diabetes 2005; 54: 3427–3434
High volume of sodium in diabetes patients leads to increased blood pressure

10% higher volume of exchangeable sodium than in non-diabetes patients without significant differences in volume of circulating plasma

SGLT2 inhibition improved insulin resistance-animal study

SGLT2 expression increased in diabetes animals

Endocrinology, March 2016, 157(3):1029-1042
Diabetologia (1987) 30:610-617
Closing highlights
Higher-risk patients with clinical ASCVD: age >65 years, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic PAD with prior MI or stroke, history of non-MI related coronary revascularization, residual coronary artery disease with >40% stenosis in >2 large vessels, HDL-C <40 mg/dL for men and <50 mg/dL for women, hs-CRP >2 mg/L, or metabolic syndrome

JACC 2017;70:1785 guidelines
GUIDELINES-2017 (NON STATIN OR ADDITIONAL LOWERING)

IMPROVE-IT (EZETIMIDE)

PCSK-9 inhibitor

Patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m2, and smoking.

Clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. The clinician–patient discussion should consider the extent of available scientific evidence for net ASCVD risk-reduction benefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration).

JACC 2017;70:1785 guidelines
CV events per year

We need better treatments

ACS-N=697 PCI

Our "life saving surgery?" not good enough

2Vdx – 2.4%
3Vdx – 4.2%

Per year

% CV event rates per year

14
12
10
8
6
4
2
0

6
4
2
0

0.8 ARR/year
1.2 ARR/year

Diabetes N=1900
Primary Prevention

<6% @ 10 yrs best

DOI: 10.1056/NEJMoa1707914 CANTOS
Thank you

Lifestyle wins
PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE

- TGRL alone no inflammation in HAEC
- TGRL enhanced inflammatory response 10x to cytokine stimulation

HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al Circ Res Feb 2007;100:000