2018 AHA/ACC Cholesterol Guidelines / A new Coronary Artery Disease Predictive Algorithm

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CARDIOVASCULAR HEALTH SOLUTIONS

DISCLOSURES

- Speakers Bureau: Verdia Clinical Laboratory, Boston Heart Labs, Amgen, Predictive Health Diagnostic Company

OUTLINE

- 2018 AHA/ACC Cholesterol Guidelines
- 2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia
- 2017 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease
- A new Coronary Artery Disease Predictive Algorithm (CADPA)

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Top 10 Take-Home Messages

2018 Cholesterol Guidelines

Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥ 50%.

Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

Top 10 Take Home Messages

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL [≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.**

   • If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable

   •If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered,
   although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.

Top 10 Take Home Messages

5. **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥ 70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.**

   In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Top 10 Take Home Messages

- 6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention have a clinician–patient risk discussion before starting statin therapy.
  - Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);
    - the presence of risk-enhancing factors (see No. 8);
    - the potential benefits of lifestyle and statin therapies;
    - the potential for adverse effects and drug–drug interactions;
    - the consideration of costs of statin therapy; and
    - the patient preferences & values in shared decision-making.

CV Risk Calculator

		Enter patient values in this column		
Risk Factor	**Units**	**Value**	**Acceptable range of values**	**Optimal values**
Sex	M (for males) or F (for females)		M or F	
Age	years		20-79	
Race	AA (for African American) or WH (for whites or others)		AA or WH	
Total Cholesterol	mg/dL		130-320	170
HDL-Cholesterol	mg/dL		20-100	50
Systolic Blood Pressure	mm Hg		90-200	110
Treatment for High Blood Pressure	Y (for yes) or N (for no)		Y or N	N
Diabetes	Y (for yes) or N (for no)		Y or N	N
Smoker	Y (for yes) or N (for no)		Y or N	N

Top 10 Take Home Messages

7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥ 7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.**

   Risk-enhancing factors favor statin therapy (see No. 8).

   If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥ 30%, and if 10-year risk is ≥ 20%, reduce LDL-C levels by ≥ 50%.

Top 10 Take Home Messages

8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).**

   Risk-enhancing factors include

   - family history of premature ASCVD;
   - persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
   - metabolic syndrome;
   - chronic kidney disease;

   - history of preeclampsia or premature menopause (age <40 yrs)
   - chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
   - high-risk ethnic groups (e.g., South Asian);
   - persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);

Top 10 Take Home Messages

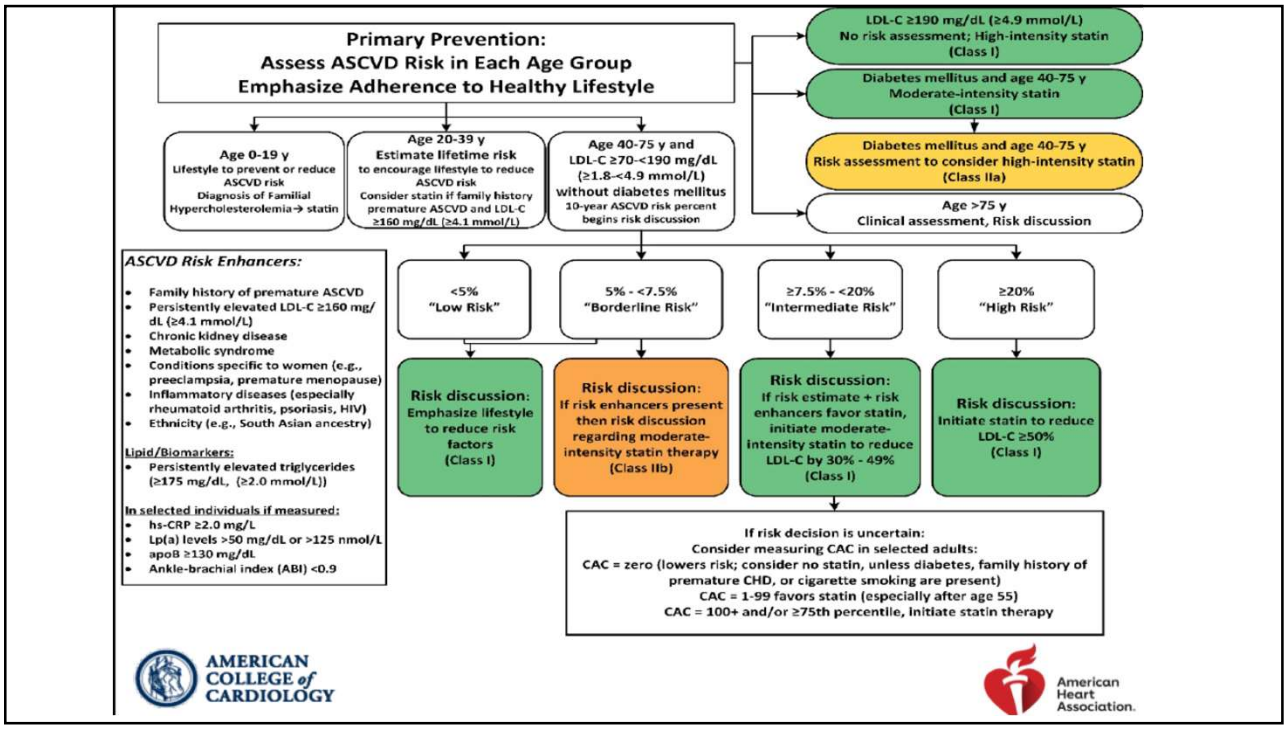
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥ 55 years of age.
- For any patient, if the CAC score is ≥ 100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy
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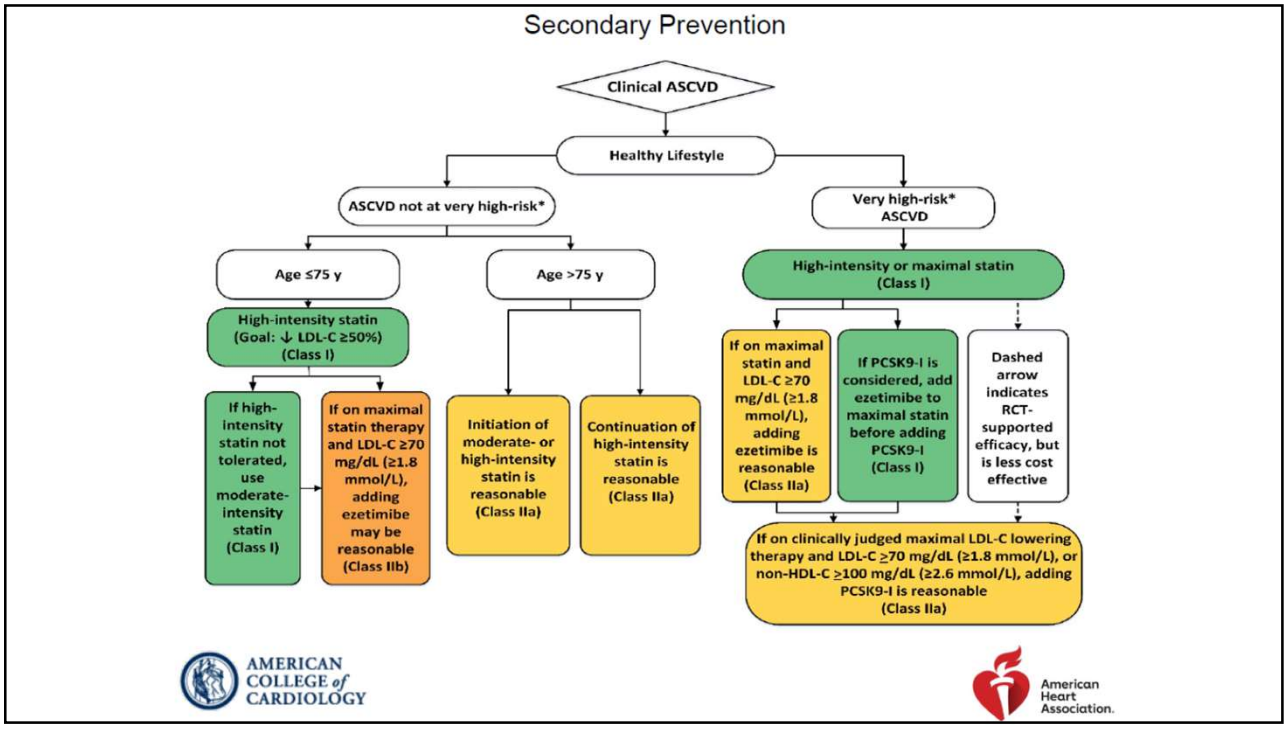
Secondary Prevention
Clinical ASCVD
Healthy Lifestyle
ASCVD not at very high-risk*
Very high-risk* ASCVD
Age ≤75 y
Age >75 y
High-intensity or maximal statin
(Class I)
High-intensity statin
(Goal: ↓ LDL-C ≥50%)
(Class I)
If high-intensity statin not tolerated, use moderate-intensity statin
(Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable
(Class IIb)
Initiation of moderate- or high-intensity statin is reasonable
(Class IIa)
Continuation of high-intensity statin is reasonable
(Class IIa)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable
(Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I
(Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable
(Class IIa)
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Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

Table 4 continued

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

National Lipid Association Recommendations

- These recommendations were published in 2015 in response to the 2013 ACC/AHA guidelines.
- These recommendations are available on phone app NLA National Lipid Association- Recommendations for Patient Centered Management of Dyslipidemia Part 1.

Major Risk Factors for ASCVD

1. Age
   - Male ≥45 years
   - Female ≥55 years
2. Family history of early CHD
   - <55 years of age in a male first-degree relative, or
   - <65 years of age in a female first-degree relative
3. Current cigarette smoking
4. High blood pressure (≥140/≥90 mm Hg, or on blood pressure medication)
5. Low HDL-C
   - Male <40 mg/dL
   - Female <50 mg/dL

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Criteria for Classification of ASCVD

- Myocardial infarction or other acute coronary syndrome
- Coronary or other revascularization procedure
- Transient ischemic attack
- Ischemic stroke
- Atherosclerotic peripheral arterial disease
  - Includes ankle/brachial index <0.90
- Other documented atherosclerotic diseases such as:
  - Coronary atherosclerosis
  - Renal atherosclerosis
  - Aortic aneurysm secondary to atherosclerosis
  - Carotid plaque, ≥50% stenosis

Sequential Steps in ASCVD Risk Assessment

1. Identify patients with either ***very high risk*** **or** ***high risk*** conditions.*

   Very High Risk
   a. ASCVD
   b. Diabetes mellitus with ≥2 other major ASCVD risk factors or end organ damage[1]

   High Risk
   a. Diabetes mellitus with 0-1 other major ASCVD risk factors
   b. Chronic kidney disease Stage 3B or 4[2]
   c. LDL-C ≥190 mg/dL (severe hypercholesterolemia phenotype)

2. Count major ASCVD risk factors
   a. If 0-1 and no other major indicators of higher risk, assign to ***low risk*** category. Consider assigning to a higher risk category based on other known risk indicators, when present.
   b. If ≥3 major ASCVD risk factors are present, assign to ***high risk*** category.

3. If 2 major ASCVD risk factors, ***risk scoring*** should be considered and additional testing may be useful for some patients.
   a. If quantitative risk scoring reaches the high risk threshold,[3] assign to ***high risk*** category.
   b. Consider assigning to ***high risk*** category if other risk indicators are present based on additional testing (see later slide).
   c. If, based on above steps, no indication is present to assign to ***high risk***, assign to ***moderate risk*** category.

*Further risk assessment is not required after identifying the highest applicable risk level.

Criteria for ASCVD Risk Categories

Risk Category	Criteria
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease Stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high risk threshold

Very High	▪ ASCVD
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage

Treatment Goals for Non-HDL-C, LDL-C, and Apo B in mg/dL

Risk Category	Treatment Goal		
	Non-HDL-C	LDL-C	Apo B
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

Recommendation of NLA Expert Panel on Treatment With PCSK9 Inhibitors

Secondary Prevention

Stable CVD + CVD RF | **ProgressiveCVD**

- ✓ Max statin + Ezetimibe
- ✓ On treatment LDL ≥70 mg/dl
- ✓ On treatment Non-HDL ≥100 mg/dl

Very-High Risk + Statin Intolerant

- ✓ Statin intolerance based on NLA expert panel
- ✓ On treatment LDL ≥70 mg/dl
- ✓ Require substantial additional atherogenic cholesterol lowering

FH

Age 40-79

- ✓ FH Phenotype
- ✓ LDL-C ≥190 mg/dl (pre treatment)
- ✓ LDL-C ≥130 mg/dl (max. tolerated treatment)
- ➢ Uncontrolled RF/markers - optional
- ➢ Genetic confirmation - optional

Age 18-39

- ✓ FH Phenotype
- ✓ LDL-C ≥190 mg/dl (pre treatment)
- ✓ LDL-C ≥130 mg/dl (max. tolerated treatment)
- ➢ Uncontrolled RF/markers

or

- ➢ Genetic confirmation

Homozygous FH

- ✓ Unknown genotype or LDL-receptor defective
- ✓ LDL-C ≥70 mg/dl (max tolerated treatment)

American Association of Clinical Endocrinologists and American College of Endocrinology

Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

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ASCVD Risk Categories

- **Low risk:**
  - No risk factors
- **Moderate risk**:
  - 2 or fewer risk factors and a calculated 10-year risk of less than 10%
- **High risk:**
  - An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%
- **Very high risk**:
  - Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH
- **Extreme risk:**
  - Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (<55 years of age for males or <65 years of age for females)
  - This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

AACE/ACE CPG. 2017;epub ahead of print; Cannon, CP, et al. *N Engl J Med.* 2015;372(25):2387-239; **Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.**

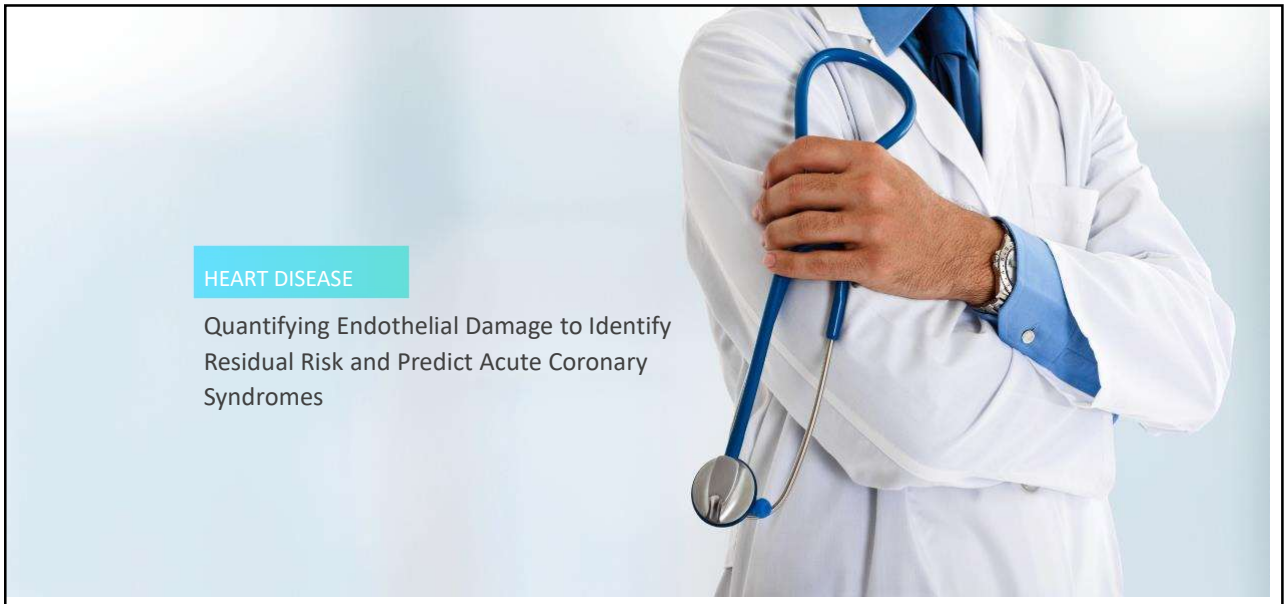
ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation*. 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; **Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497;** Lloyd-Jones DM, et al. *Am J Cardiol.* 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

A new Coronary Artery Disease Predictive Algorithm (CADPA)



Presented by
Dr. Robert Megna
Cardiovascular Health Solutions

Cardiology > Prevention

CVD Burden in U.S. Expanding Faster Than Expected

— 2015 saw levels once projected for 2030, report says

by Crystal Phend, Senior Associate Editor, MedPage Today
February 15, 2017

This article is a collaboration between MedPage Today® and:

The growth in cardiovascular disease has outpaced expectations, reaching a prevalence of 41.5% in 2015 -- 15 years ahead of schedule, according to a report from the American Heart Association (AHA).

Identifying the Vulnerable Patient

CASE STUDY

The Young Patient with Vague Symptoms

Background & Work-Up

TOM

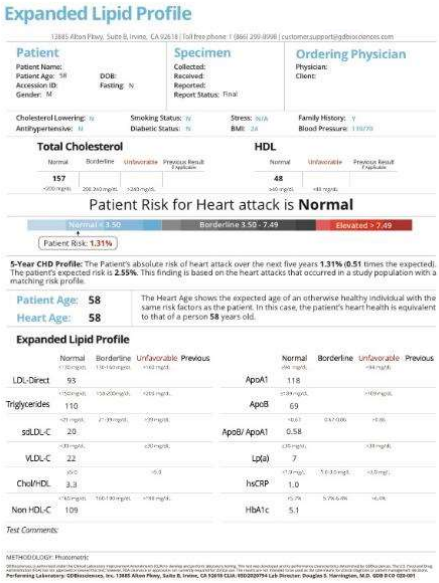
Age: 56

Patient Medical History	
Age/Sex	56 y/o Male
Smoke / Substance	No
Family History	No
Medication	No
BMI	Normal
Blood Pressure	Normal

Clinical Work-Up	Results
ASCVD Calculation (10 year)	5.4% - Normal
FRS Calculation (10 year)	7.1% - Normal

- 56 year old Caucasian male
- No family history
- Vague symptoms
- Lipids normal
- Framingham Risk normal
- American College of Cardiology Risk Calculator normal

Lipids



Expanded Lipid Profile

Patient

Specimen

Ordering Physician

Total Cholesterol

HDL

Patient Risk for Heart attack is **Normal**

Normal < 3.50 | Borderline 3.50 - 7.49 | Elevated > 7.49

Patient Risk: 1.31%

5-Year CHD Profile: The Patient's absolute risk of heart attack over the next five years **1.31%** (**0.51** times the expected). The patient's expected risk is **2.55%**. This finding is based on the heart attacks that occurred in a study population with a matching risk profile.

Patient Age: 58

Heart Age: 58

The Heart Age shows the expected age of an otherwise healthy individual with the same risk factors as the patient. In this case, the patient's heart health is equivalent to that of a person **58** years old.

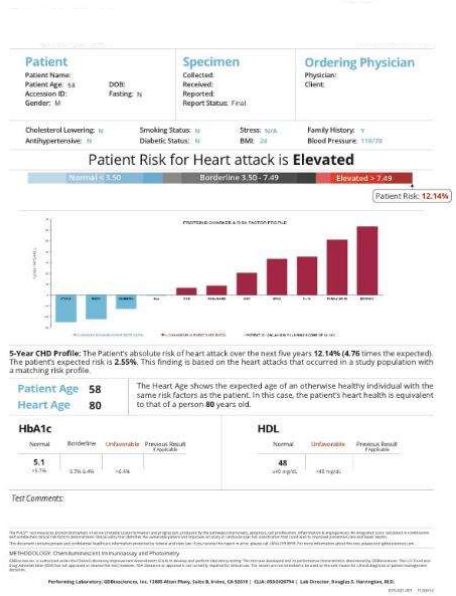
Expanded Lipid Profile

	Normal	Borderline	Unfavorable	Previous
LDL-Direct	93			
Triglycerides	110			
sdLDL-C	20			
VLDL-C	22			
Chol/HDL	3.3			
Non HDL-C	109			

	Normal	Borderline	Unfavorable	Previous
ApoA1	118			
ApoB	69			
ApoB/ ApoA1	0.58			
Lp(a)	7			
hsCRP	1.0			
HbA1c	5.1			

Test Comments:

Coronary Artery Predictive Algorith



Patient

Specimen

Ordering Physician

Patient Risk for Heart attack is **Elevated**

Normal < 3.50 | Borderline 3.50 - 7.49 | Elevated > 7.49

Patient Risk: 12.14%

5-Year CHD Profile: The Patient's absolute risk of heart attack over the next five years **12.14%** (**4.76** times the expected). The patient's expected risk is **2.55%**. This finding is based on the heart attacks that occurred in a study population with a matching risk profile.

Patient Age 58

Heart Age 80

The Heart Age shows the expected age of an otherwise healthy individual with the same risk factors as the patient. In this case, the patient's heart health is equivalent to that of a person **80** years old.

HbA1c

	Normal	Borderline	Unfavorable	Previous Result / Applicable
	5.1			

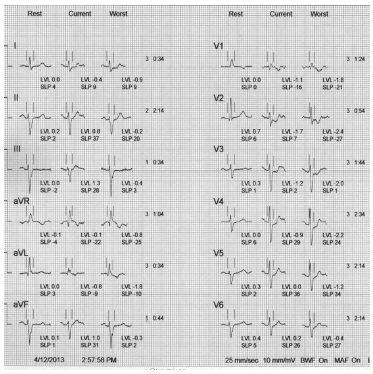
HDL

	Normal	Unfavorable	Previous Result / Applicable
	48		

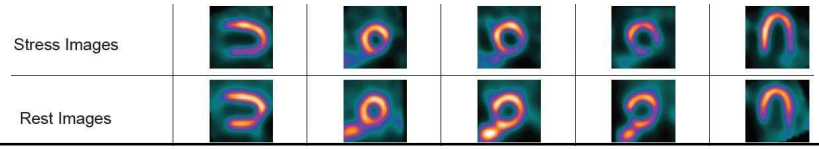
Test Comments:

Diagnostic Studies

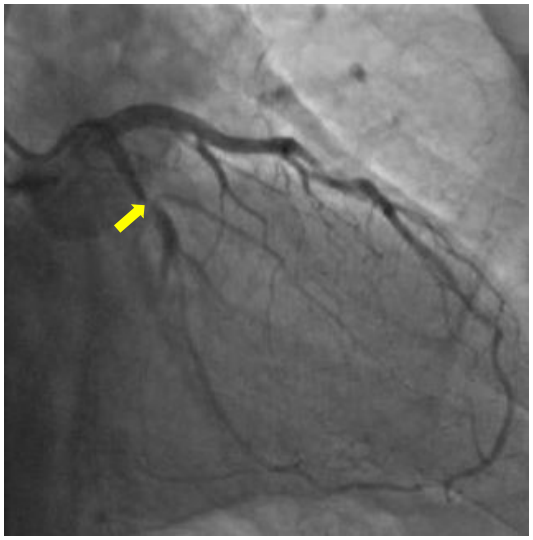
Echo stress



Perfusion Study-nuclear Medicine (lateral and inferior ischemia)



Angiography & Treatment



- >90% lesion in LCX (Left Circumflex) Artery
- Successfully stented
- Patient is doing well

Need for a Better Way to Evaluate Patients

- In 137,905 admissions for a first ACS, 83% were at **NCEP ATP III Goal** for LDLC <130
  - Sachdeva, et al. Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines. DOI: http://dx.doi.org/10.1016/j.ahj.2008.08.010
- Nearly half of all heart attacks may be silent
  - PUBLIC RELEASE: 16-MAY-2016 American Heart Association rapid access journal report
- Most physicians misclassify patient risk (nearly 66% of patient cardiac risk is underestimated)
  - 1 Kones et al., Drug Design, Development and Therapy 2011, 5:325-380
  - 2 Greenland et al., Circulation 2001, 104:1863-1867

Current Cardiac Risk Assessment Priorities

- Age
- LDL/Cholesterol
- BP
- Weight/BMI
- Smoking
- Sex
- Single Biomarkers (hsCRP, LP-PLA2, Myoglobin, etc.)
- Framingham, ASCVD Calculator, Reynolds etc.

Actual Contributing Risk Factors is a Much Longer List Partially Represented Below

- Stress
- Infections (Flu,Bartonella, Lyme's,H.Pylori, Leptospirosis,HIV, Hepatitis, etc.)
- Diet (Sugar, Trans Fats, Refined Carbs, Deep Fried Foods, Etc.)
- Lack of Exercise
- Too much Exercise
- Inflammatory Bowel Disease/IBS
- Metabolic Syndrome
- Family Hx
- Substance Abuse (Alcohol, Opioids)
- NSAIDs
- Proton Inhibitors
- Psychoactive Drugs (Anti-Depressants, Bipolar Rx)
- Cancer
- Cancer Rx
- Depression
- Autoimmune Diseases
- Psoriasis
- COPD
- Pollution
- Microbiome Alterations
- Hormone abnormalities
- Vitamin Deficiencies
- Oral Hygeine

Endothelium

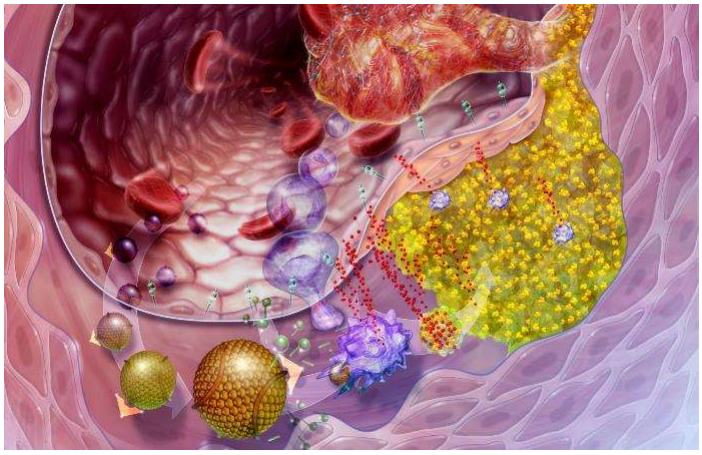
- The **endothelium**, which forms the inner cell lining of all blood vessels and lymphatics in the body, is a spatially distributed organ. The **endothelium** weighs approximately 1 kg in the average patient and covers a total surface area of 4000 to 7000 square meters.

- If you were to tear off and spread out the average adult's skin, it would cover **approximately 22 square feet** (**2 square meters**).

Coronary Artery Calcification, Epidemiology, Imaging Methods, and Clinical Implications" the American Heart Association Science Advisory and Coordinating Committee on June 20, 1996

Inflammation

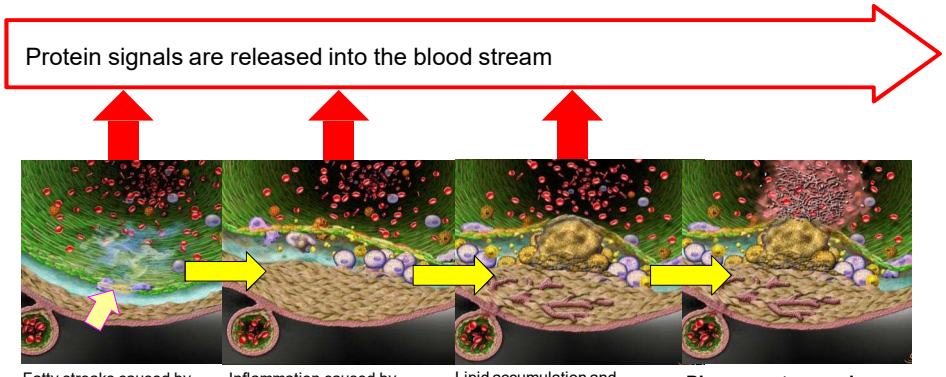
- The body's response to injury or infection



Coronary Artery Calcification, Epidemiology, Imaging Methods, and Clinical Implications" the American Heart Association Science Advisory and Coordinating Committee on June 20, 1996

Progression of Cardiovascular Disease

Vulnerable plaque forms progressively involving multiple biological pathways



Fatty streaks caused by lipid oxidation from free radicals form in arterial wall

Inflammation caused by oxidized lipids in the arterial wall results in tissue damage and fibrosis

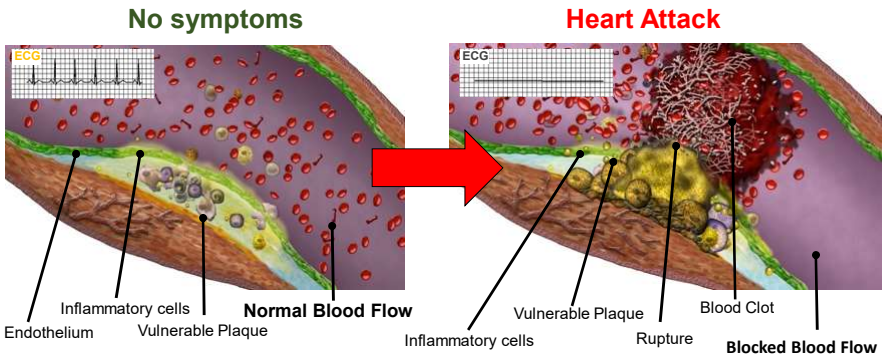
Lipid accumulation and inflammation increase forming **Vulnerable Plaque**

Plaque rupture and blood clot formation → **Heart Attack**

No single biomarker is sufficient to detect this process; **multiple biomarkers are needed**

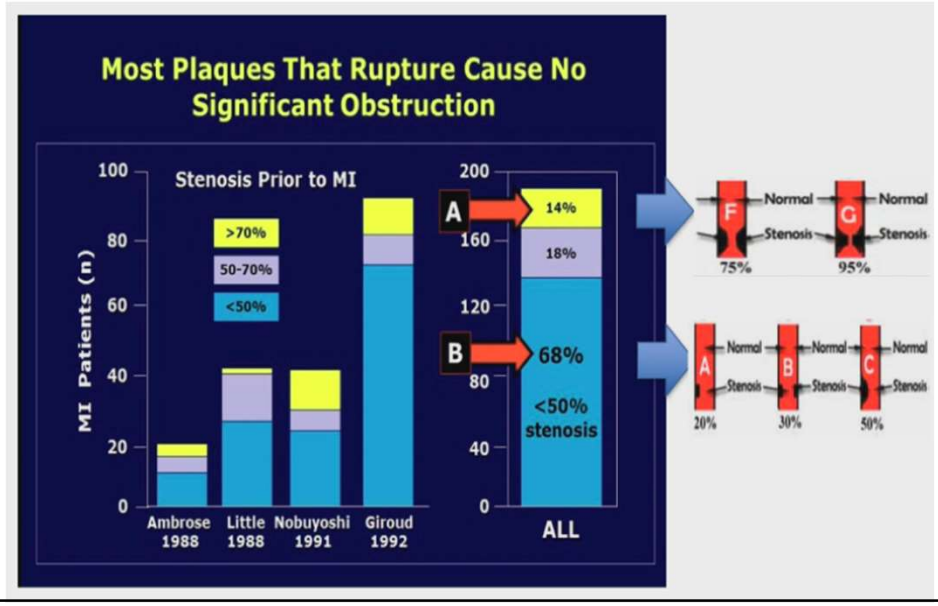
Page 5

75% of Heart Attacks are Caused by Unstable lesion Rupture and a Blood Clot in a Coronary Artery



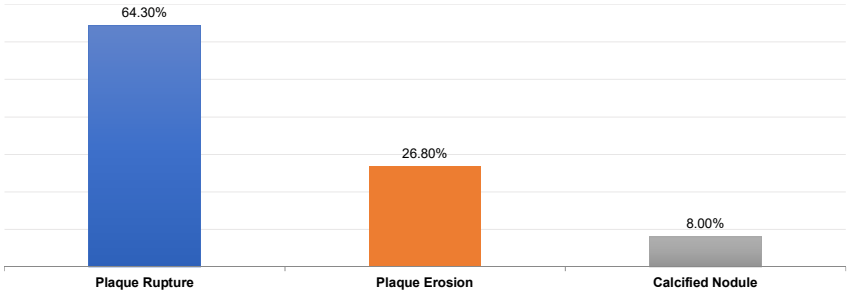
Detecting an unstable lesion before it ruptures identifies individuals with a heart attack risk and allows time to take action

Source: AHA, JAMA



STEMI Studies with IVUS & OCT

(Optical Coherence Tomography)



Plaque Rupture (64.3%)
- These had less fibrous plaque
- Thin cap
- Greater plaque burden
- Dominant in men and women >50 years.

Plaque Erosion (26.8%)
- Greater plaque eccentricity
- Large lumen
- 54% more likely to have calcification, deeper calcium, a break of calcium sheet into lumen
- More constrictive lumen with mild inflammation (younger women).

Calcified Nodule (8.0%)
- Greater than ½ have negative remodeling
- Calcium sheet: superficially located large calcification
- Older individuals

Higuma, et al. JACC vol. 8, No. 9 1166. 2015.

MODULE 2:

Coronary Artery Disease Predictive Algorithm (CADPA)

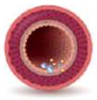
✓Quantify Endothelial Damage

✓Identify Residual Risk

✓Predict ACS

Atherosclerosis Biology

Process of chronic endothelial injury increases permeability of the arterial wall
- Allows free radicals (i.e. oxidized lipid particles) to aggregate on the arterial surface
- Initiates the formation of lesions (atheroma)[1].



Endothelial injury stimulates production of signaling molecules
- Recruits leukocytes (monocytes, granulocytes, and T-cells) to the injury site
- Stimulates the proliferation of smooth muscle cells [2,3].

Recruited leukocytes transform into lipid-laden foam cells and expand the lesion[4].
- Growth factors are released
  - Stimulate the generation of new capillaries through angiogenesis
  - Provides the growing lesion with an adequate blood supply.

Expression of adhesion molecules/chemokines (MCP-1 and others) induce platelet, lymphocyte and monocyte adhesion, further activating the lesion injury.

Smooth muscle cells alter and hypertrophy
- Apoptosis produces excessive amounts of collagen, elastin and proteoglycans
- Transforms the lesion into a fibrous plaque
  - Comprised of a lipid core and thin fibrous cap (unstable lesion or vulnerable plaque)[5].

Atherosclerosis Biology

- Calcium score (CAC) is a surrogate marker for total burden of plaque but does not detect soft non-calcified lesions
- The CADPA Cardiac Test detects endothelial damage and disease activity in soft lesions complementing CAC
- Total plaque burden summation =

CADPA

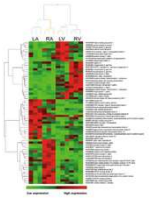
CAC

- 1) necrotic core + 2) fibro-fatty + 3) fibrous plaque + 4) calcification.

- Plaque frequently is in transition at different rates from
  - 1) necrotic core→2) fibro-fatty→3) fibrous→4) dense calcium
- Statins accelerate this transition

9 Protein Unstable Lesion Signature Validation (CADPA)

Gene expression work Identified over 250 proteins expressed in mice and humans in vulnerable coronary plaque tissues



Narrowed proteins to those detectable in serum by immunoassay, including all clinically used biomarkers like MPO, hsCRP, and LP-PLA2 along with all global risk factors

Validation: **NHLBI** applied the 9 biomarker assessment to a second population **MESA** and confirmed the findings

The 9 biomarker algorithm predicts who is at risk for ACS in a 5 year period

All three systems confirmed **9 biomarkers and the 4 global risk factors**

1. Method of Akaike
2. Bayesian Method
3. Drop-in Deviance

Three different statistical software systems tested **permutations of biomarkers** and **global risk factors** to identify sub-clinical disease and predict ACS

- Bayes' theorem converts the results from your test into the real probability of the event.
- Deviance is a **goodness-of-fit** statistic for a statistical model
- The Akaike information criterion (AIC) indicates the relative quality of statistical models for a given set of data.

Path to Verification

Study	Population Summary	Significance
Advance/Kaiser	**3179 adult individuals** **Cases: 398 (post MI or UA)** **Control: age 60 to 72 no history of CAD**	Proof of Concept AUC=.92
Orentriech/Kaiser	**1390 adult individuals** **Cases: 695 (MI or UA)** **Controls: Matched case-control** **(average age: 62 years)**	1. Ranked Biomarkers 2. Optimum Algorithm Size 3. HR: 13.0
PMRP Marshfield Clinic	**20,000 members (age range: 40-80 years)** **Cases:362 (MI or UA)** **Controls: 722 (disease free at baseline and during the entire study)**	Prognostic Algorithm Discovery
MESA	**7000 individuals (age range: 45-85)** **Case individuals: 179 (CAD)** **Controls: 495 (CAD free during study)**	Verification and Transportability
CADPA Observational Study	**9,146 Individuals** **Cases: n/a** **Controls: Patient is own control**	1. Predictors of Risk in Diabetics 2. Predictors of High Risk
Total	**40,715**	

CADPA Cardiac Test Performance in MESA

5,731 Patients
222 Events

- Serum frozen 5-8 years earlier tested to predict who would have an ACS
- All patients were disease free at admission by MESA standards

Normal Values have a 97% Negative Predictive Value

61% of patients who experienced an ACS detected

Cardiac Algorithm

- 13 component algorithm serum blood test
  - Multiplex of 7 unique proteins related to endothelial injury
  - 2 proteins from an auto-channel instrument
  - 4 global risk factors
- Validation required comparison to traditional and single analyte risk factors, and other multivariate risk tools
  - hsCRP
  - Framingham
  - Reynolds
- Statistical validity and comparative performance was determined by cNRI (clinical net reclassification index)
- Algorithm was developed in 5 cohorts representing 41K patients and externally validated in MESA(cNRI=43%)

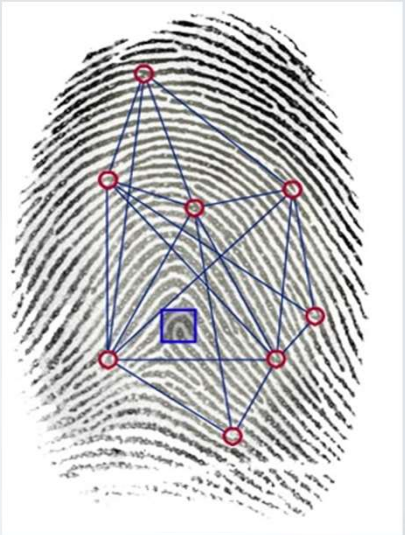
Optimal Identification of Early Disease Requires an Algorithm

The Fingerprint Model

Accuracy of Identification

- **1 point match = 2%**
- **2 point match =4%**
- **3 point match = 8%**
- **4 point match = 20%**
- **5 point match = 35%**
- **6 point match = 70%**
- **7 point match = 84%**
- **8 point match = 92%**
- **9 point match = 98%**

Unique signature of Proteins or Points



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9 Proteins Are Signficant

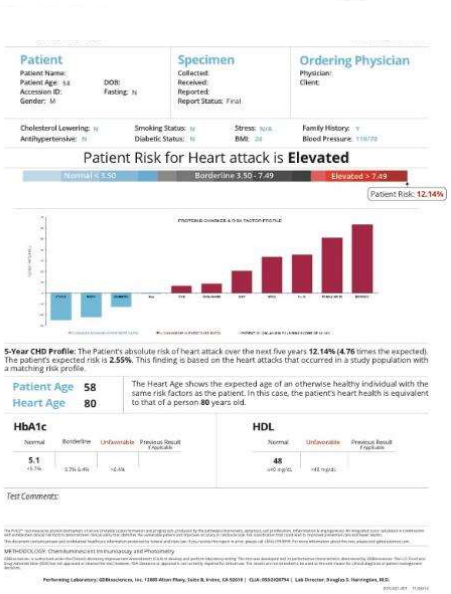
9 clinically-significant protein biomarkers to measure the body's immune response to arterial or endothelial damage leading to unstable lesion formation and potential rupture.

Relation to Endothelial Damage & Unstable Cardiac Lesions	
MEASURES FORMATION & FREE RADICAL DAMAGE	
IL-16	"Signaling Molecule" triggers repair process. Immune response begins.
MEASURES IMMUNE RESPONSE	
MCP-3	Recruits monocyte/macrophages that form foam cells which clean up damaged cells, lipids, and cellular debris.
Eotaxin	Recruits eosinophils that consume fibrin and prevent blood clots.
CTACK	Recruits T-cells that regulate the local inflammatory response at the site of the lesion.
MEASURES PROGRESSION	
sFas	Cell repair "prevents cell death".
Fas Ligand	Initiates cell death and recycling.
HGF	Forms collagen. Stimulates tissue and repair.
MEASURES CLINICAL RISK FACTORS	
HDL	Helps remove bad cholesterol and neutralizes free radicals.
HbA1c	Diabetes marker.

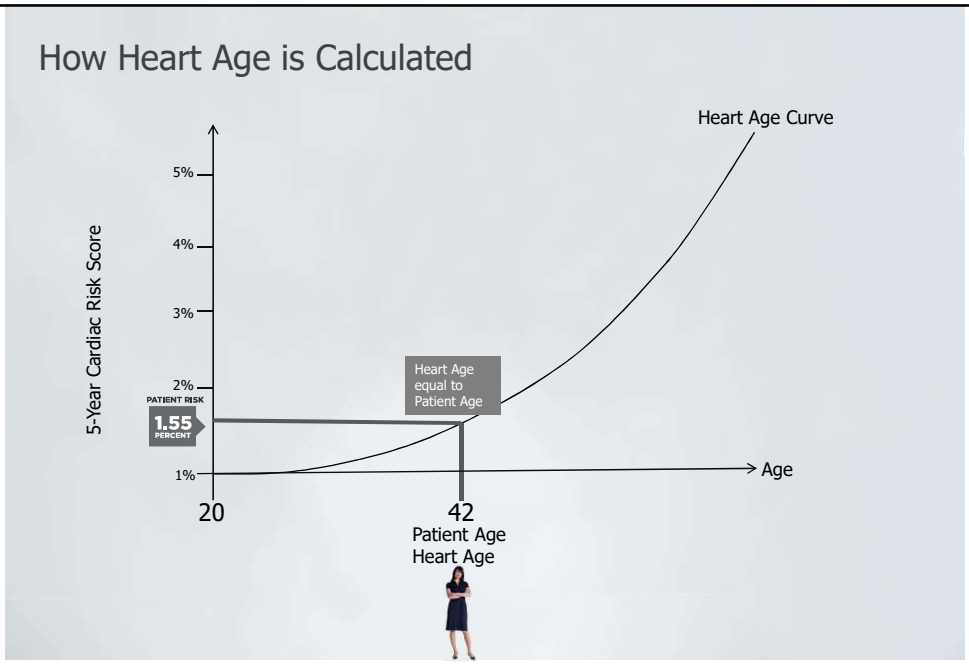
CADPA Biomarker Univariate Clinical Utility

Biomarker		
IL-16	Elevated levels of endothelial-derived microparticles, and serum CXCL9 and SCGF-β are associated with unstable asymptomatic carotid plaques (Scientific Reports 5, Article number: 16658;2015)	Cutpoints from 13,891 patients **A high score is protective in the presence of asymptomatic Carotid Plaques**
	The Role Of Microparticles in Carotid Disease heartjnl-2014-306118.179	
MCP-3 Presence of CAD MCP-3 alone better than FRS+-CRP AUC .70 vs 0.60	Circulating chemokines accurately identify individuals with clinically significant atherosclerotic heart disease (Physiol Genomics 31: 402–409, 2007.)	Cutpoints from 13,891 patients
CTACK	Elevated levels of endothelial-derived associated with unstable asymptomatic carotid plaques (Scientific Reports 5, Article number: 16658-2015)	Cutpoints from 13,891 patients
EOTAXIN CAD and number of lesions	Association of plasma eotaxin levels with the presence and extent of angiographic coronary artery disease Atherosclerosis 186 (2006) 140–145	Cutpoints from 13,891 patients
sFAS	Increased Soluble Fas Plasma Levels in Subjects at High Cardiovascular Risk (Arterioscler Thromb Vasc Biol 2007;27:168-174.)	Cutpoints from 13,891 patients
FAS Ligand	Increased Soluble Fas Plasma Levels in Subjects at High Cardiovascular Risk (Arterioscler Thromb Vasc Biol 2007;27:168-174.)	Cutpoints from 13,891 patients **A high score is protective**
HGF Stroke rate per 1000-Pt Years	**<809 pg/mL 809-1011 pg/mL >1011 pg/mL** **1.64 2.6 5.43** Hepatocyte Growth Factor Is Positively Associated With Risk of Stroke MESA (Multi-Ethnic Study of Atherosclerosis) (Stroke . 2016;47:2689-2694.)	Cutpoints from 13,891 patients

Coronary Artery Predictive Algorith



How Heart Age is Calculated



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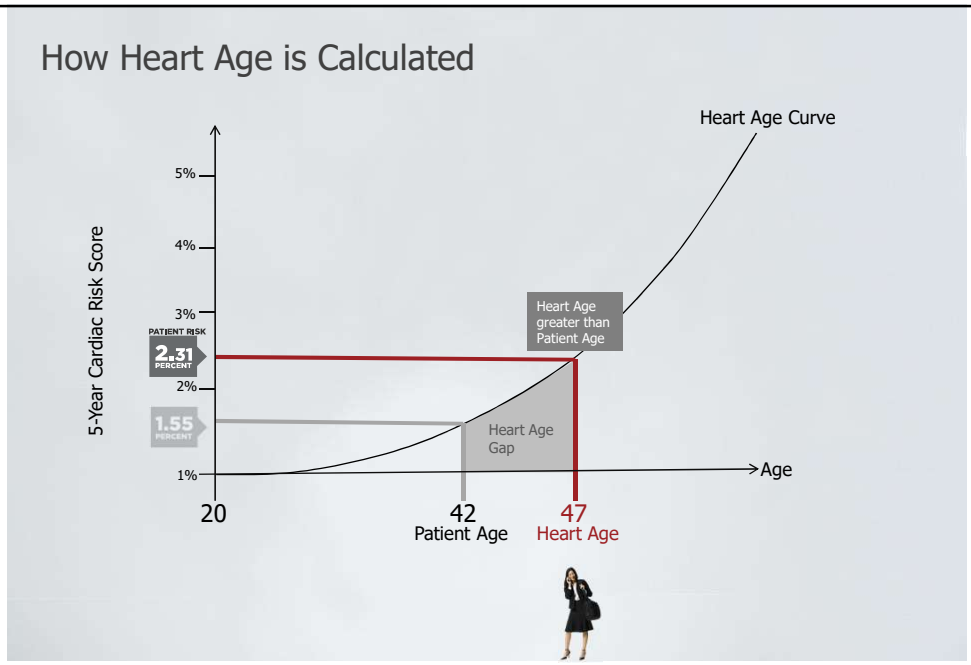
How Heart Age is Calculated



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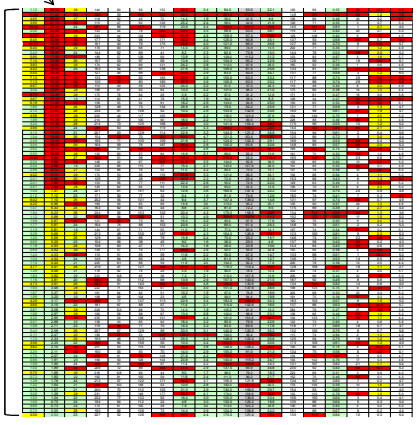
Identifying the Vulnerable Patient Improve Patient Care

CADPA Cardiac Test

Observational Study

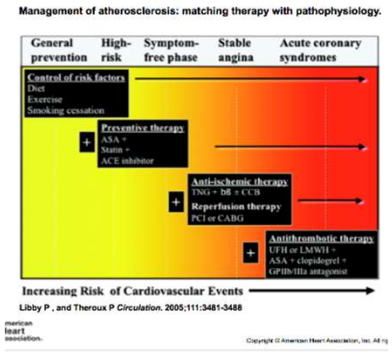
100 Patient from 4 Cardiologists



Equivalent to Framingham or AHA/ACC risk calculation currently the gold standard in Cardiac Risk Assessment

Individual Biomarkers that are currently being used for surrogate biomarkers

Clinical Application



MODULE 3:

Clinical Application in Identifying the Vulnerable Patient

Who needs to have CADPA testing? When do you need to run it?

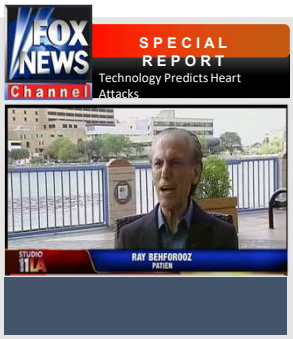
- Primary prevention
- 40 yo and greater — can still do for <40 on case by case basis
- Positive family history - importance of a good case history
- Those with traditional cardiovascular risk factors
  - AHA guidelines
  - Asymptomatic, don't realize their changeable risk factors and may require motivation
- Highly stressed, sedentary (or over-exercisers)
- Smoking/alcohol/substance abuse
- Women with endometriosis
- Those that are interested in baseline health studies and monitoring - include this in your preventative health care treatment plans
- Second opinion for those prescribed drug therapy and want to know if this is best option
- Etc.

Source:

CASE STUDY

Asymptomatic CAD-Chronic Total Obstruction

Background



Age: 78
Retired IT Professional

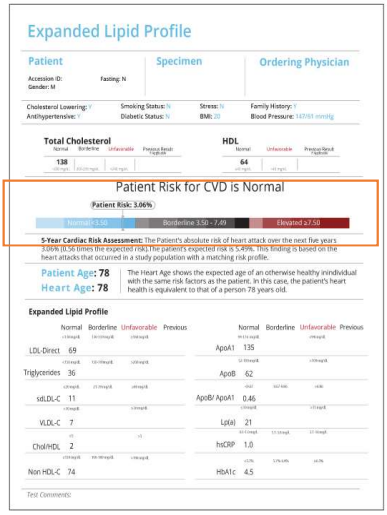
Patient Medical History	
Stress	Yes
Smoke / Substance	No
Family History	Mother had MI at 56 y/o
Medication	Previous Blood Pressure medication
BMI	Normal (20.0)
Blood Pressure	Normal (147/61)
EKG	NSR
Prev. CADPA Risk Assessment	1 year prior Results Borderline (3.6%)

- 78 y/o Middle Eastern male retired IT professional who had "no specific complaints" but was seen at his primary care doctor due to his daughter's concern that he seemed unmotivated and tired.
- The patient did indicate that he had been under excessive stress in the last year due to his family.

Preliminary Work-Up

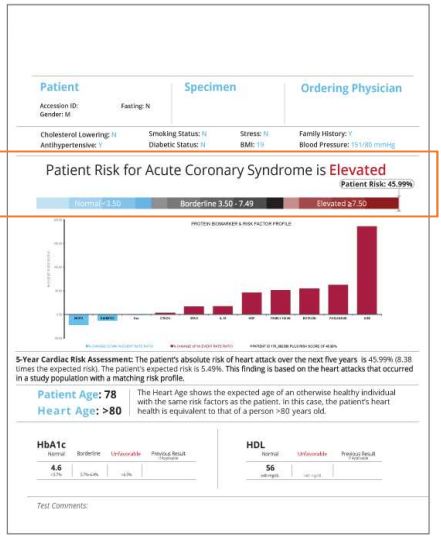
Clinical Testing	Results
Labs All Normal Total non-HDL Cholesterol sdLDL LDL ApoB	NSR
CIMT	Mild intimal thickening

- Lab testing was performed but was normal
- CIMT results showed mild intimal thickening.
- HMO Primary Care doctor felt patient was stable.
- Patient was discharged without further work-up
- Daughter took patient to out-of-network cardiologist



Preliminary Work-Up

- Out of network Cardiologist performed the CADPA Cardiac Test
- Results showed patient at 8.34x expected risk for an Acute Coronary Syndrome (ACS) for his age and an absolute 5-year score of 45.99% (expected 5.49%)



Additional Work-Up

Clinical Testing	Results
CAC	600
Stress Test	Unable to perform due to knee problem
Angiography	Roughly 100% Blockage

- Further studies were performed:
  - CAC test 600
  - Unable to perform a stress test due to knee problem
- The patient was referred back to the original primary care physician who referred him to the in-network cardiologist
  - The patient underwent angiography that identified near 100% Blockage aka “widow-maker”
  - An interventional procedure (stent) was performed

Additional Work-Up

Clinical Testing	Results
CAC	600
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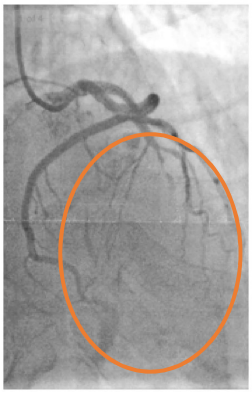
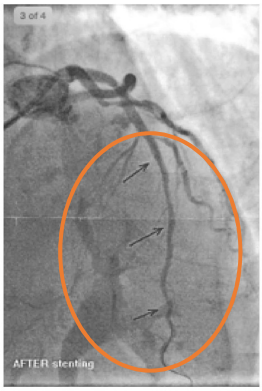
Before & After Stent



Pre-Stent
Almost 100% blockage of main artery



Post-Stent
Healthy blood flow

Treatment & Follow-Up

Follow-Up Medications	
Clopidogrel 75 mg	75 mg
Aspirin (baby)	81 mg
Atorvostatin	10 mg
Atenolol	25 mg

- Patient placed on medication regimen.
- Patient is currently doing well.
- Exercise tolerance and energy level back to "normal".

CASE STUDY

Asymptomatic “Macho Man” Confounding Symptoms

Background

JOHN

Age: 47

Special Forces

Patient Medical History	
Hypertension	No
Smoke	No
Family History	Father had MI at 44 y/o
Medication	No
Diabetic	No
Hyperlipidemia	No
BMI	Overweight 29.4
Blood Pressure	Normal
Weight	188 lbs
Pulse	70
Total Cholesterol	202
LDL	140
HDL	41
Lp(a)	7.1
Hs-CRP	0.7
EKG	NSR

- 47 y/o Caucasian male Special Forces soldier with sporadic precordial left chest and shoulder pain since 2005
- Patient had history of multiple combat-related injuries including a left clavicular fracture with mal-aligned healing in 1992

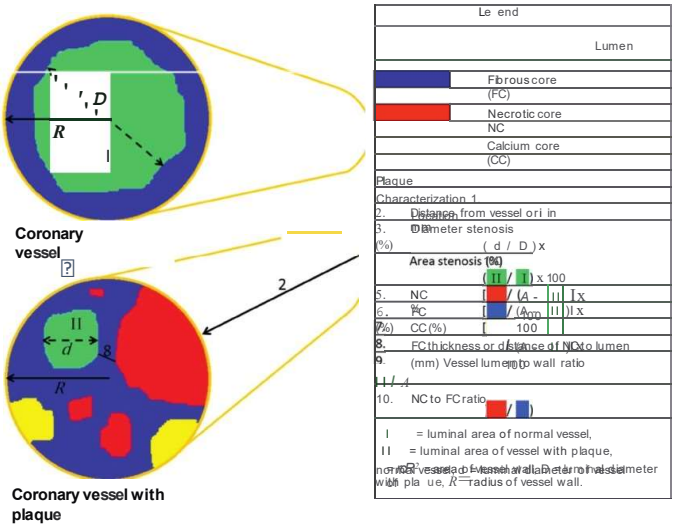
Preliminary Work-Up

- Negative treadmill stress test
- ACC/AHA Score 5.5% (normal)
- Framingham Score 7% (normal)
- C-IMT normal
- Echocardiogram performed
  - Trace PI, NSR, normal
- CADPA Cardiac Test performed due to patient family history Results:
  - CADPA Score elevated 8.07% (High Risk of ACS)
  - 5.34x expected risk (1.51%)

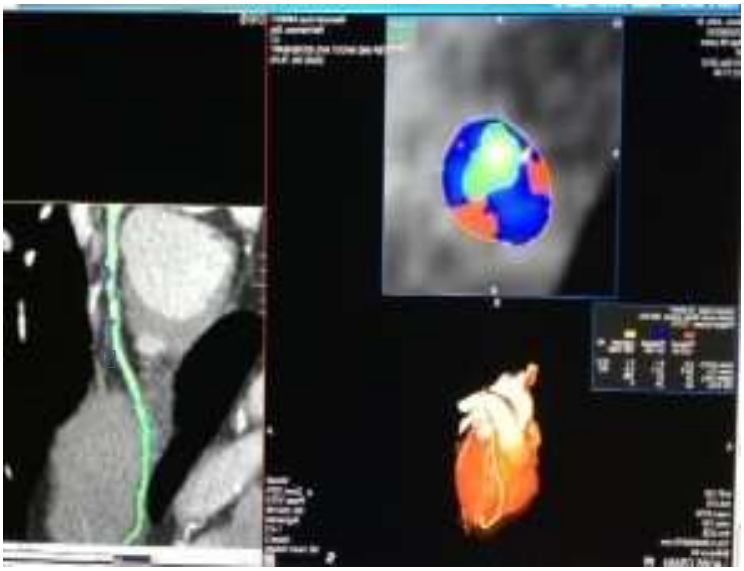
Clinical Work-Up	Results
EKG	NSR
Echocardiogram	Trace PI NSR Normal left ventricular contractility – EF 83% Left ventricular hypertrophy at 15.3 (athletic heart)
C-IMT	Normal
Stress Test	Negative
ASCVD Calculation (ATP IV)	5.5%
FRS Calculation	7%
CADPA Cardiac Test	Score 8.07% 5.34x expected score (expected score 1.51%)

CTA Performed

FIGURE 1. Plaque parameters used for characterization via coronary computed tomography angiography.



CTA LAD



Treatment & Follow-Up

Follow-Up Medications	
Clopidogrel 75 mg	Loading dose 600 mgs 75 mgs daily
Aspirin (baby)	325 mgs
Atorvostatin	40 mgs daily
Metoprolol succinate	50 mgs daily

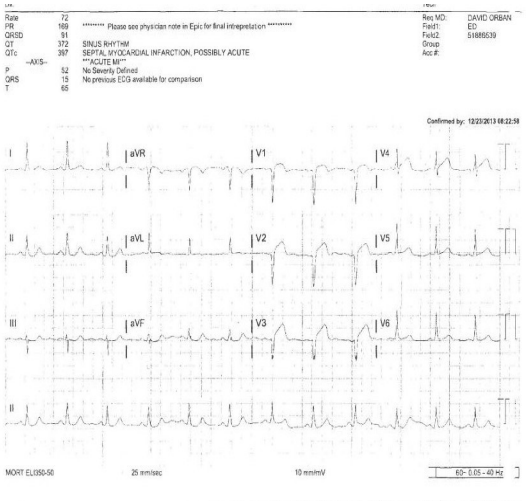
- Patient initiated aggressive medical therapy
- Patient scheduled for left heart cardiac catheterization with PCI on Monday following his Friday clinic visit to review findings because he was asymptomatic

Disease Course

- Patient delayed initiation of his recommended medical therapy over the weekend because he “felt fine”
- Approximately 48 hours after follow-up of Coronary CTA, patient began having burning sternal pain and diaphoresis while playing video games which continued for over 30 minutes
- Patient’s wife called EMS against patient’s wishes for further evaluation

EKG at Tampa General Hospital

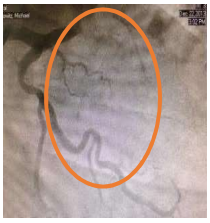
EKG by EMS revealed a STEMI (Heart Attack) in the anterior lateral leads



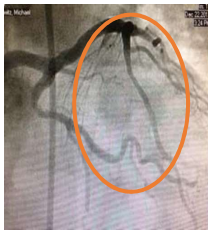
Work-Up

Echocardiogram:

- During STEMI – markedly depressed EF with akinesis of the anterior lateral walls extending down to the apex
- 48 hours past PCI-complete resolution of the abnormal territories with normalization of LV function

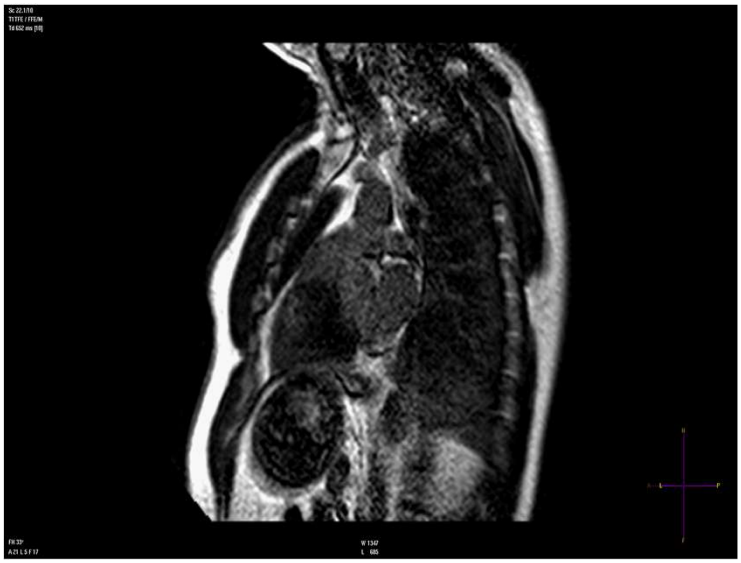


Before

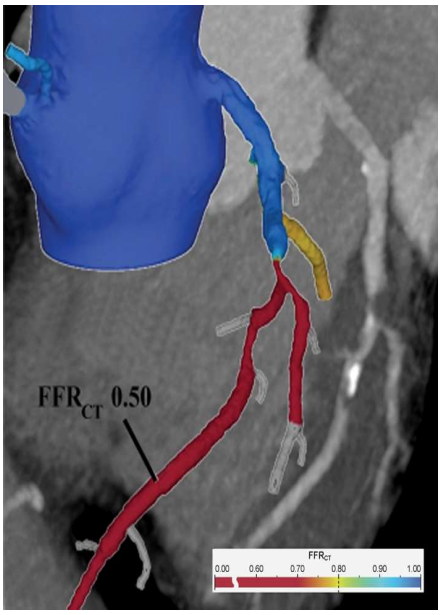


After

Cardiac MRI



FFR Results



When CADPA is ELEVATED:

- Counsel your patient about the meaning of the test, risks
- Counsel yourself about the meaning of the test, risks
- Respond to the risks and entire CLINICAL PICTURE as necessary

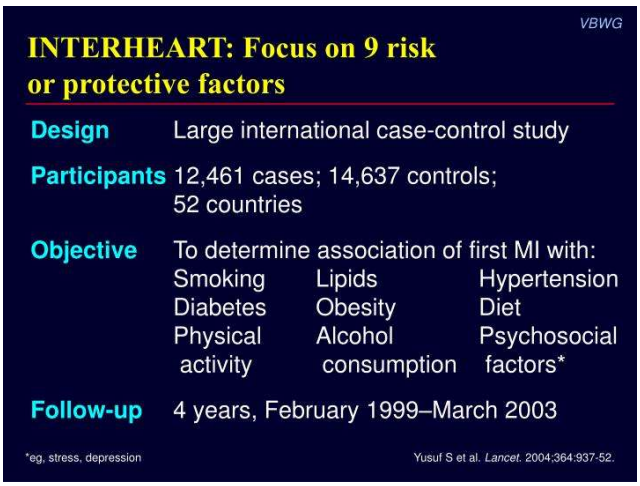
Source:

PREVENTION

80% of Heart Disease is Preventable with
5 Healthy Lifestyle Modifications

When individuals know important information about their heart health, they are empowered to make critical lifestyle changes that can save their life

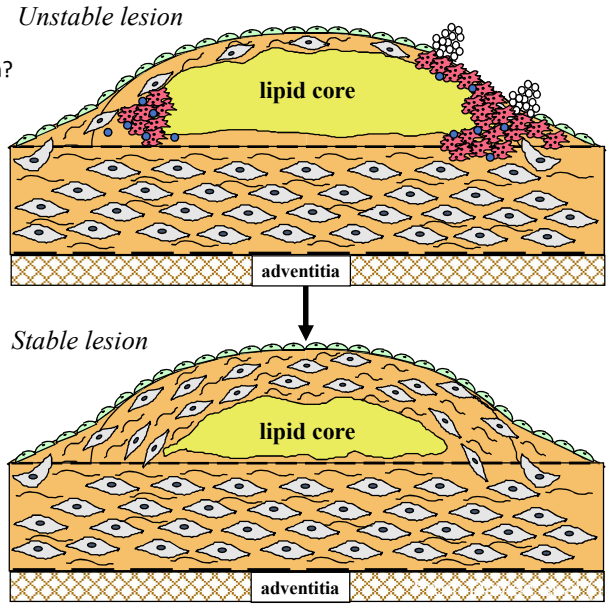
Interheart Study



Goal of Therapy

What facilitates this conversion?

- Statin pleiotropic effect
  Empagliflozin
- Liraglutide
- Olive oil
- Avocado oil
- Mediteranean diet
- Aged garlic extract
- Berberine
- Nicotinamide Riboside
- Omega 3 fish oil
- Vit D
- Riboceine
- Glutathioceine
- Resistance training
- Etc.



What can we do about it?

- MCP-3: reduced with
  - Quercetin[1]
  - Calcium channel blockers (amlodipine, manidipine)[1]
  - Leukotriene receptor antagonists (LTRA's)[1]
  - Doxycycline[1]
  - Trichostatin A (reversible inhibitor of histone deacetylase (HDAC); anti-tumor, epigenetic oncologic agent, antioxidant)[1,2]
  - Curcumin (MCP-1, 3, TNF-alpha)[3, 5]
  - Rosmarinic acid (MCP-1)[6]
    - Highest plant sources: Melissa, Mint (peppermint, spearmint), Sage (common, Russian)[7]
  - LDN[4]

Source:

What can we do about it?

- FAS (reduced with):
  - Growth hormone[1]
  - Atorvastatin (10-80mg/d; low to moderate starting-dose)[2]
- Fas Ligand: minimal effects with atorvastatin[2]
- Eotaxin (reduced with):
  - Resveratrol (also confers chemoprotective, chemotherapeutic, CVD/oxid. stress/anti-inflammatory)[3], can slow progression of wide range of age-associated diseases
    - Sources: red wine, grapes, passionfruit, white tea (piceatannol same)
    - Dose: 200-400mg
  - Piceatannol (Resveratrol metabolite)[3]
  - Curcumin[4] (also lowers SBP, similar to effects of aerobic exercise 30-60min)[8]
- CTACK (reduced with):
  - NAC (reduction of proinflamm cytokines, leukocyte infiltration)[5,6]
  - AI protocol (glutathione, rosmarinic acid, AIP diet, etc)
- HGF (reduced with):
  - Curcumin[7]

Source:

What can we do about it?

- IL-16 (modulate with):
  - Stress reduction
  - Weight loss/exercise
  - Sleep apnea treatment
  - Anxtioxidants (resveratrol, melatonin, ALA, NAC)
- HDL (increased with):
  - Exercise
  - Healthy fats (omega 3, plant mono/poly, Mediterranean diet)
  - Reduced etOH
  - Smoking cessation
- HbA1c (reduced with):
  - Berberine
  - ALA
  - Chromium
  - Gymnema
  - NAC (improves glucose tolerance, reduces hepatic steatosis, ACEI (reduces angiotensin II by 50%))[1]

Source:

What can we do about it?

- Nutrition:
  - Portfolio diet
    - Soy (50g), Almonds/walnuts (30g), soluble fibre (20g), plant sterols (2g)
    - Reduces TC and LDL-C without negatively affecting fat-soluble vitamins/compounds[3]
    - Reduces non-HDL cholesterol, apolipoprotein B, triglycerides[4]
    - Reduces SBP and DBP[4]
  - Mediterranean diet
    - Nuts (walnuts, mixed) – plaque stabilization (30g/d, >3d/week)[6]
    - Vegetables
  - Olive oil
  - Avocado oil
  - Walnuts
    - Reduce LDL-C by ~9-16%[5]
    - Reduce DBP by 2-3 mmHg[5]
    - Improve endothelial function, decrease oxidative stress, increase cholesterol efflux[5]
  - Ground flax seed (enterolignans, omega 3,6)
    - Antihypertensive: Patients with SBP >140 mmHg achieved 15mmHg reduction in SBP, 7mmHg in DBP; less than 140 SBP achieved ~10/7 mmHg reduction; dose of 30g per day for 6 months[1]
    - Cholesterol lowering effects (TC, LDL-C)[2]
    - Prolonged decrease in ghrelin (5g-10g + per day)[2]

Source:

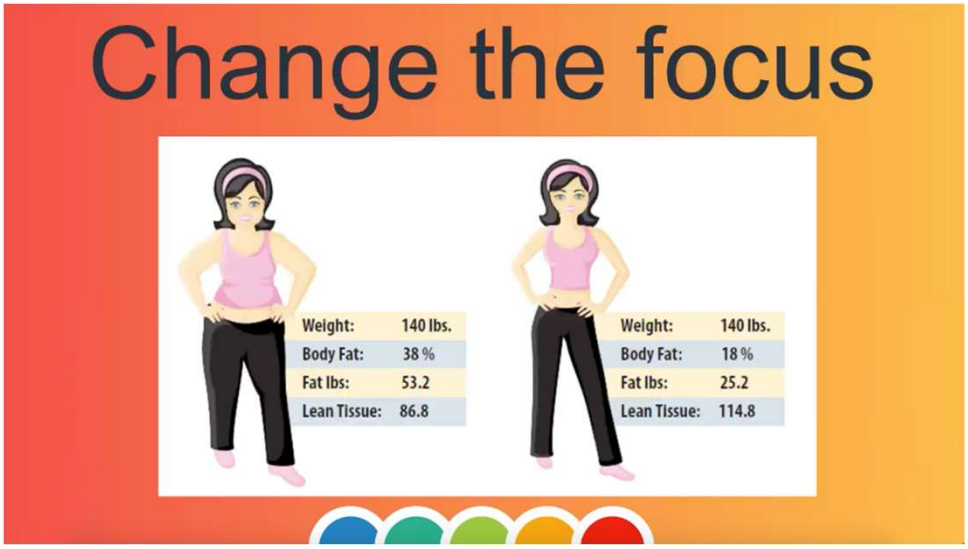
Treatment Continued (my favourites)

- Dietary:
  - Portfolio Diet
  - Plant-based, MUFAs/PUFAs
  - Ground flax seed
- Nutraceutical/botanical:
  - Omega 3 oils - 4g+ of EPA+DHA
    - Reduced nonfatal stroke, nonfatal MI, cardiovascular death (4g EPA)[3], decreased perioperative bleeding with increased n-3-PUFA levels[4]
  - CoQ10 – 300mg
  - Curcumin – 2g
  - NAC (1200mg BID)/Glutathione – reducing oxidative damage, preserve endothelial function[5]
  - Hawthorn
  - Magnesium
  - L-Carnitine – 2-4g
  - D-Ribose – 5-15g (ischemic heart disease, post-MI, CHF)[1]
- Lifestyle:
  - Exercise - aerobic and **resistance** training; continued is important – lose effect on endothelium after 1 month of detraining[2]
  - Dry sauna
  - Meditation
  - Shinrin-yoku

Treatment Continued

- Residential "greenness" – based on normalized difference vegetation index (NDVI)[1]
  - Associated with lower levels sympathetic activation
  - Reduced oxidative stress
  - Higher angiogenic capacity

- Sauna – 2-3x/week (5-30 minutes)[2]
  - Reduces risk of dementia, sudden cardiac death
  - Reduces SBP and/or DBP
  - Improves HRV
  - Improved flow-mediated arterio- and vasodilation of blood vessels
  - Reduces levels of Epi/Norepi
  - Increased levels of NO metabolites in blood and urine
  - Decreased total cholesterol & LDL
  - Decreased FPG
  - Cellular level: increased heat shock proteins
    - Reduced ROS
    - Increased NO bioavailability
    - Increased insulin sensitivity
    - Reduced oxidative stress and inflammation


Change the focus
Weight: 140 lbs.
Body Fat: 38 %
Fat lbs: 53.2
Lean Tissue: 86.8
Weight: 140 lbs.
Body Fat: 18 %
Fat lbs: 25.2
Lean Tissue: 114.8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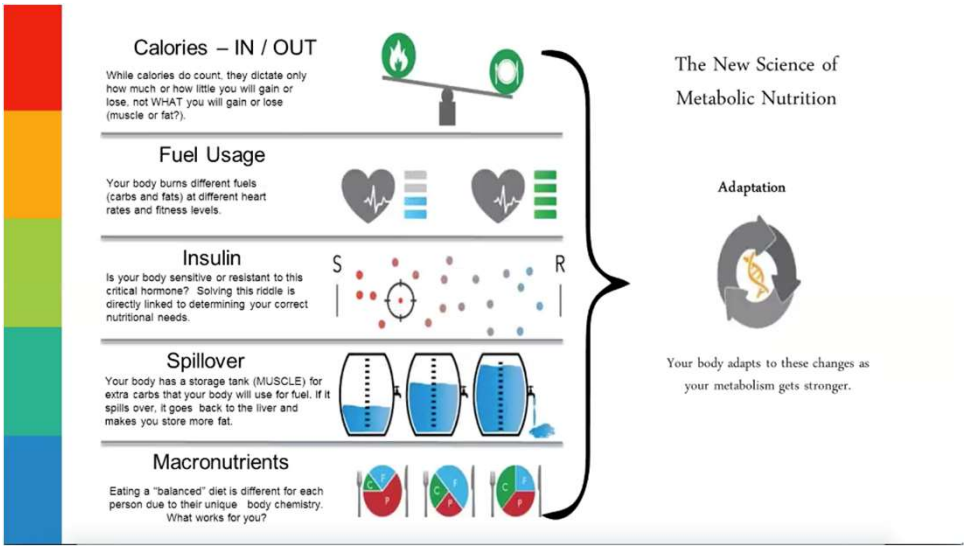
Losing fat - good
Quick fix weight loss
Losing muscle - bad
Studies show
55%
of weight loss is muscle

Exercise:What Does Science Say?

Afterburn and Safety

- Afterburn: both HIIT and weight training produced more afterburn than cardio for up to 21hours post-exercise
- Weight training has so many benefits already, any afterburn we do get is like the shiny gold and hot-rod red accents on Iron Man's suit: not as functional as the sweet hand and feet repulsors that allow Tony to fly and fight bad guys, but still awesome
- **The biggest caloric gains and losses ultimately happen in the kitchen**: (Nothing can make up for EBOC: Excess Brunching Over Coffee/Champagne.) You can't outrun your fork
- In one study there were 64 cardiovascular complications during training—63 occurred during aerobic training, and only one event occurred during strength training. **Based on this study, strength training is a much safer form of training for heart disease patients, especially in regards to being safe for the heart.**



exercise

The GOAL of exercise is METABOLIC ACTIVATION, NOT "burning calories"!

POWER
Exercises that involve compound movements (multi-joint or whole body)
i.e. Deadlifts
GOAL - build stronger tendons, ligaments and bones

TARGETED STIMULUS
Exercises that specifically target a particular muscle group
i.e. Pec Dec flyes for chest
GOAL - build new lean muscle tissue

METABOLIC STIMULUS
Exercises that involve multi-joint motions involving one or more body parts and multiple joints OR are explosive
i.e. Bench jumps, Low cable squat and row
GOAL - improve muscular endurance and fat burning

METABOLIC CONDITIONING
10 Minutes of HIIT (High Intensity Interval Training) or a combination of the two
i.e. A: Elliptical, Treadmill...
B: Burpees, Jump Rope...
GOAL - improve heart and lung capacity, increase fat burning

Does Lifestyle Modification Work??

CASE STUDY

The Physician Who "Took it to Heart"

Background

DR. SMITH

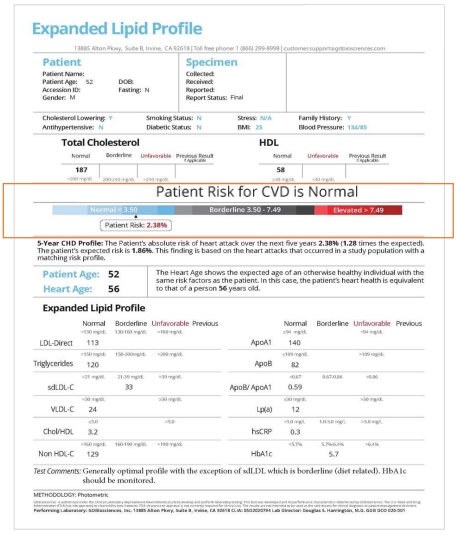
Age: 52

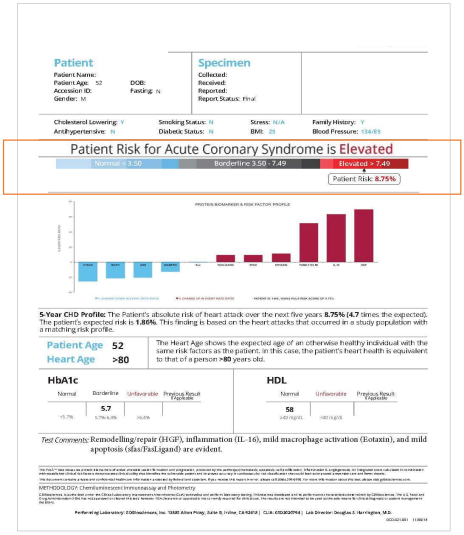
Physician

Patient Medical History	
Hypertension	No
Smoke / Substance	No
Family History	Yes
Medication	Cholesterol-lowering
Diabetic	Pre-diabetic
Hyperlipidemia	No
BMI	26
Blood Pressure	Pre-hypertension - 134/85

- 52 y/o physician
- Aware of "pre-diabetic" status
- Has focused on his cholesterol levels
  - Lipids Normal
  - HbA1c Borderline at 5.7%
- 5-year CVD risk: Normal (2.38%)
- 10-year ASCVD: Normal (3.6%)

Lipid vs. CADPA





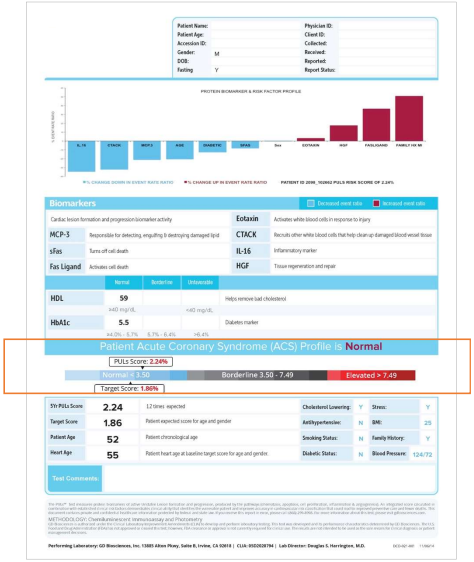
CADPA Follow-Up Results

Follow-up CADPA results showed the physician had reduced his risk from 8.75% to Normal at 2.24% in 4 months with a lifestyle-only prescription:

1. Brisk walking 30" 3X/week
2. Resistance training with 12# kettle ball and 10 pound dumbbells 30" 3X/week
3. Cut out sugar and refined white carbs

Results:

1. 16 pound weight loss
2. HbA1c normal for first time in 10 years
3. CADPA normal



THANK YOU! QUESTIONS?

Robert Megna D.O., M.S.,
FNLA, FMNM, FAARFM
ABoIM, AOBFP, ABIHM, ABAARM
Diplomate, American Board of Clinical Lipidology
Certified Hypertension Specialist

CARDIOVASCULAR HEALTH SOLUTIONS

CASE STUDY

The CEO Who
Toned it Down

Background

Mr. CEO

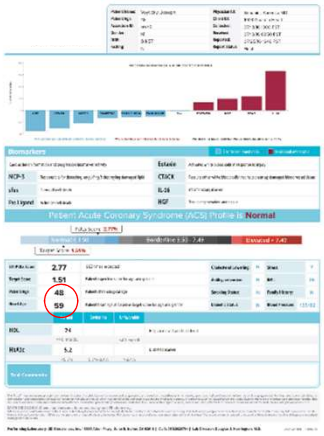
Age: 48
CEO

Patient Medical History	
Hypertension	No
Smoke / Substance	No
Family History	Yes
Medication	None
Diabetic	No
Hyperlipidemia	No
BMI	26
Blood Pressure	Normal

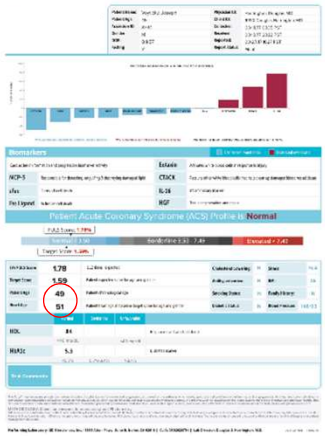
- 5-year CVD risk: Normal (2.38%)
- 10-year ASCVD: Normal (3.6%)

CADPA vs. CADPA 2 Mths. Later

Before



After



CASE STUDY

Native American Lifestyle Modification Project

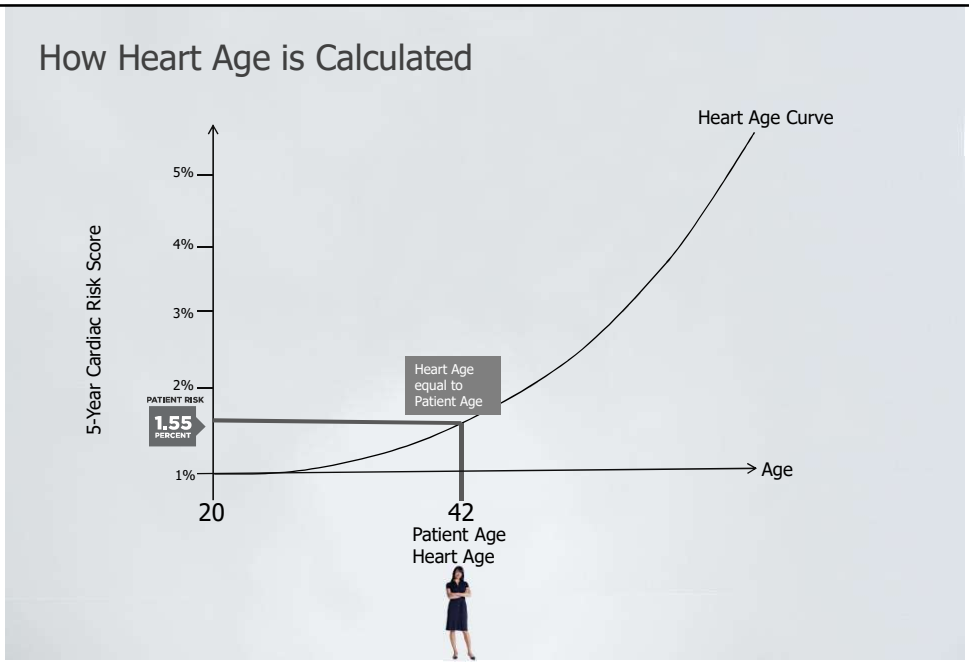
Native American Lifestyle Modification

CADPA vs. CADPA 1.5 Yrs Later

Before

After

How Heart Age is Calculated



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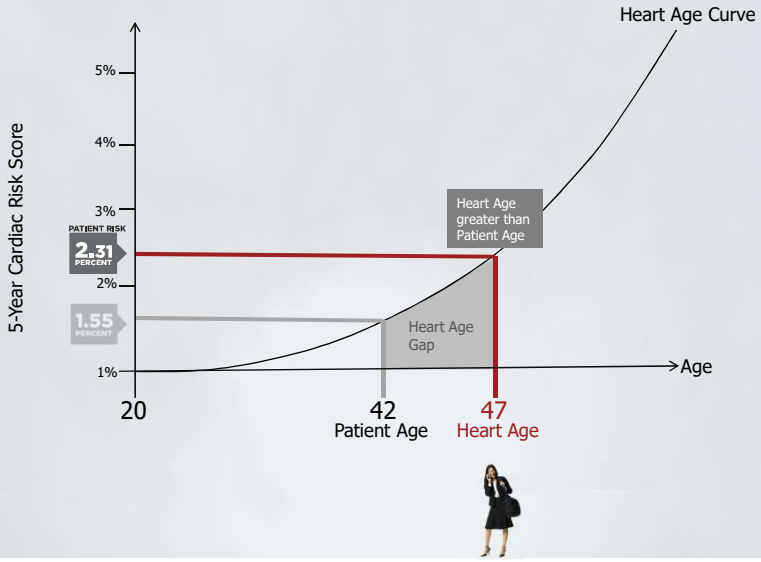
How Heart Age is Calculated



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Extra Slides

Estimating Clinical Value

Clinical Net Reclassification Index (cNRI)

- The performance metric that we used was the **Clinical Net Reclassification Index (cNRI)**[4], which measures the improvement in risk classification that a new method introduces with respect to an existing method
  - cNRI = % of subjects correctly reclassified - % of subjects incorrectly reclassified
  - Performance for cases and controls is evaluated separately (like sensitivity and specificity)

$$\text{CNRI} = \frac{(\text{Cases Up - Cases Down})}{\text{Cases in Risk Category}} + \frac{(\text{Controls Down - Controls Up})}{\text{Controls in Risk Category}}$$

- The cNRI is derived by applying the new method to a subset of the population that can benefit the most from an improved method of identifying its true risk
  - For cardiovascular disease, the Risk Category subset is the **intermediate risk** population, as defined, for example, by the Framingham
- Applying the CADPA Cardiac Test to individuals defined as being at intermediate risk by the Framingham resulted in a **cNRI of 43% (p<.001)** in our validation study

Page 10

CADPA Biomarker Univariate Clinical Utility

Biomarker		
IL-16	Elevated levels of endothelial-derived microparticles, and serum CXCL9 and SCGF-β are associated with unstable asymptomatic carotid plaques (Scientific Reports 5, Article number: 16658;2015)	Cutpoints from 13,891 patients **A high score is protective in the presence of asymptomatic Carotid Plaques**
	The Role Of Microparticles in Carotid Disease heartjnl-2014-306118.179	
MCP-3 Presence of CAD MCP-3 alone better than FRS+-CRP AUC .70 vs 0.60	Circulating chemokines accurately identify individuals with clinically significant atherosclerotic heart disease (Physiol Genomics 31: 402–409, 2007.)	Cutpoints from 13,891 patients
CTACK	Elevated levels of endothelial-derived associated with unstable asymptomatic carotid plaques (Scientific Reports 5, Article number: 16658-2015)	Cutpoints from 13,891 patients
EOTAXIN CAD and number of lesions	Association of plasma eotaxin levels with the presence and extent of angiographic coronary artery disease Atherosclerosis 186 (2006) 140–145	Cutpoints from 13,891 patients
sFAS	Increased Soluble Fas Plasma Levels in Subjects at High Cardiovascular Risk (Arterioscler Thromb Vasc Biol 2007;27:168-174.)	Cutpoints from 13,891 patients
FAS Ligand	Increased Soluble Fas Plasma Levels in Subjects at High Cardiovascular Risk (Arterioscler Thromb Vasc Biol 2007;27:168-174.)	Cutpoints from 13,891 patients **A high score is protective**
HGF Stroke rate per 1000-Pt Years	**<809 pg/mL 809-1011 pg/mL >1011 pg/mL** **1.64 2.6 5.43** Hepatocyte Growth Factor Is Positively Associated With Risk of Stroke MESA (Multi-Ethnic Study of Atherosclerosis) (Stroke . 2016;47:2689-2694.)	Cutpoints from 13,891 patients

Exercise:What Does Science Say?

Weights

- The addition of muscle strengthening activity into the physical activity recommendations is due to emerging scientific evidence linking this type of activity to **reduced risk of type 2 diabetes**, **high blood pressure**, **weight gain, physical disability, heart disease, poor musculoskeletal and mental health and premature death**.
- Among the most important roles muscle strengthening activity has is enabling older adults to **keep their physical functioning adequate**, preventing or delaying frailty and falls, and thus maintaining independent living for longer.
- Importantly, when compared to aerobic physical activity such as walking and cycling, weight training has greater benefits for bone/joint health, the ability to perform activities of daily living (general mobility, getting into and out of a chair, bathing, dressing) and **slowing the loss of skeletal muscle mass/strength**. These outcomes are very important for all age groups, especially for older adults as we seek ways to maintain their independence.