Risk Assessment for Primary Prevention

AKA Some of You Won’t Get a Second Chance to Make a First Impression

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Alternative Title:
The Tension Between Population Medicine and Personalized Medicine

How can we assess and stratify risk?

- Risk Factor Evaluation
- Lab Testing
- Imaging

Risk Factor Evaluation

- Current guidelines recommend office-based risk stratification of all individuals using multiple risk factor scores to determine global risk

- An expanding number of readily accessible assessments of global cardiovascular risk have been widely available to health care practitioners for decades.

Risk Calculators

- Framingham
- Reynolds’s Risk Score
- HEARTSCORE
- AHA/ACC Pooled Cohort Equation (PCE)

Framingham Risk Score

- The gold standard
- Developed in 1998
- Uses:
  - Age
  - Total Cholesterol
  - HDL-C
  - Smoking
  - Blood pressure
  - History of diabetes mellitus
Estimates sex-specific risk of coronary heart disease (CHD) events over the subsequent 10 years

Each individual’s risk can then be categorized as low, intermediate, or high (<10%, 10%-20%, and >20%)

Other Risk Scores

- Reynolds risk score
- Incorporate the use of biomarkers (hsCRP)
- Family history of premature CHD.

- European Scores:
  - PROCAM6
  - HEARTSCORE
  - Both are variations of the Framingham score

ACC/AHA Pooled Cohorts Equation

- This new calculator incorporated:
  - Sex
  - Total Cholesterol
  - Age
  - HDL
  - Race
  - Systolic Blood Pressure
  - Smoker?
  - Rx for HTN?
  - Diabetes?

ACC/AHA “PCE”

- Different than Framingham:
  - Added endpoint of Stroke to non-fatal MI and CHD death
  - Expanded applicability to different ethnic groups

Fact:

- There is solid evidence that if you modify the variables that comprise global CHD risk assessment tools, you will decrease CV disease.
  - Smoking cessation
  - Blood pressure control
  - Physical activity
  - Lipids

Great. So what’s the problem?
Fact:

- Surprisingly, there is no clear evidence that simply providing patients with global CHD risk information actually improves:
  - Risk perception
  - Adherence to therapy
  - Improvements in cardiovascular outcomes

The Problem with Calculators

Despite the presence and use of these scores, in 50% of patients the initial manifestation of CAD is an MI or death

In 1/3 it is sudden death

The Problem with Calculators

Part II

- The majority of CV events occur in patients deemed “low risk” by these calculators
  - Data from NHANES suggests that low risk patients comprise 85% of the population
  - Constitute 2/3rds of the population risk

In the “Real” World

- A majority of patients hospitalized with CAD have LDL-c levels that are “normal” by current guidelines
  - 50% of patients with a first ACS event had LDL levels < 100 mg/dL
  - 17% had LDL < 70

The Problem with Calculators
Part III

- Patients continue to have clinical events
- Despite being at their recommended targets
- Despite having “normal” lipid panels
- Despite being on treatment

In substantial numbers

Our current process of risk assessment is not adequate

We need improved identification of at-risk individuals

A path to a more “personalized” risk assessment

How else can we stratify risk?

- Risk Factor Evaluation
- Calculators
- Lab Testing
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Lab Testing for Risk Stratification

- Lipid Testing
  - ApoB
  - NMR
- CardioCRP/hsCRP
- CardioDx “Corus CAD” Test

But is this really risk assessment, or just more accurate lipid assessment?

hsCRP

- Acute phase protein produced predominantly by hepatocytes
- Non-specific marker of inflammation
  - Can be produced by inflamed endothelium as well
  - Inflammation from a variety of different causes appears to increase CV risk
  - May not be “just” a marker of inflammation, but also a participant

Relative Risk of CV Events According to Baseline Levels of hs-CRP in Healthy Postmenopausal Women

- Just a marker, or is the level important?
  - There is a gradient of increasing risk proportional to hs-CRP beginning at extremely low levels of CRP
  - Hs-CRP of 0.2 is better than 0.5 which is better than 1.5
  - Jupiter confirmed that patients who achieved lower hs-CRP levels did better
hs-CRP

- Reducing both hs-CRP and LDL-C is beneficial
  - PROVE-IT-TIMI 22
  - CARE
  - REVERSAL
  - A to Z
  - JUPITER

hs-CRP

- Lowered by:
  - Weight Loss
  - Increased exercise
  - Smoking cessation
  - Statins

hs-CRP

- Still somewhat controversial whether it is an independent risk factor
- No evidence yet that lowering CRP lowers risk or improves outcomes independent of lowering LDL

Lipid Testing
- ApoB
- NMR
- CardioCRP/hsCRP
- Genetic Testing

Gene Presence?
- 9p21
- Lp(a)

Gene Expression?
- CORUS CAD

CIRT is a randomized, double-blind, placebo-controlled, multi-center, event-driven trial funded by the National Heart Lung and Blood Institute (NHLBI) that will enroll 7,000 men and women from the United States and Canada.

While inflammation plays a critical role in atherothrombosis, it is unknown whether inhibition of inflammation per se will lower vascular event rates.

Evaluate whether or not low-dose methotrexate (LDM) will reduce rates of myocardial infarction, stroke, and cardiovascular death among stable coronary artery disease patients with type 2 diabetes or metabolic syndrome, conditions associated with an enhanced pro-inflammatory response.
Corus CAD

- Integrates age, sex and gene expression to calculate a score that has been demonstrated to accurately assess the likelihood of obstructive CAD
- Production of RNA changes in response to disease states
- High Sensitivity (89%)
- High Negative Predictive Value (96%)
- Designed for use in evaluation of pts with chest pain


How else can we stratify risk?

- Risk Factor Evaluation
- Calculators
- Lab Testing
- Imaging

Risk Stratification via Imaging

- Stress Tests
- CT Angiography of Coronary Arteries
- Cardiac MRI
- Cardiac PET Scan
- Calcium Scoring

A Word About Stress Tests…

- Who thinks we should use stress tests to risk stratify primary prevention patients?

DIAD Study

- 1123 asymptomatic diabetic patients randomized to screening with nuclear stress testing or to no screening.
  - Ischemia was detected in 25% of patients
  - Severe abnormalities in approximately 6% of patients.
  - Patients were then followed for ~5 years.
  - There were 15 events in the screening group and 17 events among those who weren't screened
    - Statistically nonsignificant
    - No difference in any of the secondary end points
    - angina, heart failure, stroke, and revascularizations.

Young LH et al. JAMA 2009; 301: 1547-1555
Why?

- Established noninvasive methods of evaluating CAD, such as stress testing, only identify patients with advanced atherosclerotic disease that are flow-limiting and cause myocardial ischemia.

- But autopsy studies show that most fatal events come from non flow-limiting lesions.
  - Rupture of “vulnerable” plaques that were not previously flow-limiting.

- We need a better way to identify who has sub-clinical atherosclerosis.

Risk Stratification via Imaging

- **Stress Tests**
- **CT Angiography of Coronary Arteries**
- **Cardiac MRI**
- **Cardiac PET Scan**
- **Calcium Scoring**

**CT Angiography of the Coronaries**

- **Pros:**
  - Available
  - Accessible
  - Able to see within coronaries
    - Can see composition of plaque
- **Cons:**
  - Cost
  - Radiation exposure

**Cardiac MRI**

- **Pros:**
  - Great for overall structure of the heart
  - Pathology of myocardium
- **Cons:**
  - Duration
  - Cost
  - Can’t see within coronaries due to motion

**Cardiac PET**

- **Pros:**
  - The best stress test
  - Excellent performance in detection of ischemia, viability
  - Excellent in obese patients
- **Cons:**
  - Duration
  - Cost
  - Availability
  - Don’t actually visualize within coronaries
  - Can’t see subclinical atherosclerosis
Risk Stratification via Imaging

- Stress Tests
- CT Angiography of Coronary Arteries
- Cardiac MRI
- Cardiac PET Scan
- Calcium Scoring

Calcium Scoring

Calcium Scoring: What actually is it?

- ECG-triggered, low-radiation, non-contrast CT scan
- 3mm Slices

- Allows detection and quantification of the amount of coronary artery calcium (CAC)
- Coronary calcium is defined as a lesion above a threshold of 130 Hounsfield units, with an area of $\geq 3$ adjacent pixels (at least 1 mm$^2$).

Calcium Scoring is Accurate

- The presence of calcium in coronary arteries is pathognomonic of atherosclerosis
- Coronary calcium is 100% specific for coronary atherosclerosis

Coronary Calcium Scan

- Coronary Calcium
  - Measured by Agatston score
  - Equivalent mass and volume
  - Reproducible, semi-automatic computer method
  - Result compared to population norms

In common practice, the scores are expressed as a percentile score based on age and sex

- Use one of the many available databases
  - MESA, Framingham, etc.
Accurate for Atherosclerosis

- Atherosclerotic plaque burden and the extent of CAC are closely correlated
- Intravascular ultrasound
- Post-mortem autopsy
- Histopathology
- The total CAC score measured represents an anatomic measure of overall cardiac plaque burden

Budoff MJ et al. JACC 2008 Nov 18;52(21):1724-32

Background

- CAC is proportional to the extent of atherosclerosis
- The extent of coronary atherosclerosis, rather than the severity of an individual stenosis, is the most important predictor of death due to CV causes

Schmermund et al 1997

Why Extent and Not Severity?

- Because most fatal events come from non flow-limiting lesions
  - Rupture of “vulnerable” plaques that were not previously flow-limiting
- The more lesions you have, the higher risk for rupture of one of them

CAC provides the most accurate available method of the early detection of atherosclerosis
- “The Bethesda conference”

Topts A et al. JACC 2002; 41:1860-2

Calcium Scoring for Risk Stratification

Calcium Scoring is Prognostic

- There is a linear relationship between CAC and CHD events
  - The higher the score, the worse the prognosis
  - Scores in the highest quartile predict a significantly increased risk of a cardiac event
    - > 2x for women
    - >10x for men
  - Even after adjustment for NCEP ATP III category
“Negative Risk Factor”

- cIMT <25th percentile
- Absence of carotid plaque
- Brachial Flow-Mediated Dilation >5% change
- ABI >0.9 and <1.3
- hsCRP <2
- Homocysteine <10
- NTproBNP <100
- No microalbuminuria
- No FamHx of premature CAD
- Absence of metabolic syndrome
- Healthy Lifestyle

The strongest negative risk factor was CAC = 0

Calcium Scoring is Prognostic

- CAC = 0:
  - Patients have a very low rate of CV death or MI (~0.4%)
  - Across ethnicities
  - Up to 12 years out
  - Overall 15-year mortality rate was ~3%

The Power of Zero

- In >64,000 asymptomatic patients
  - Only 146 of 25,903 patients (0.56%) had a CV event during a mean follow-up period of 51 months
Even in older patients:
- Those with absent or low CAC are at a significantly lower risk of mortality compared with the general population.

However, when CAC > 0:
- In patients with any detectable calcium, their 3-5 yr CHD risk of events is nearly 4-fold higher.
  - CAC 1 to 10 (1.06%)
  - CAC >10 (3.96%)
- May not be quite high enough for secondary prevention, but clearly should have aggressive risk factor modification.

Coronary Calcium Scoring
- Among individuals at “intermediate risk”, a calcium score of >100 (> 75th percentile for age) would yield a post-test probability of >2% per year.
  - High risk
    - ~ CHD risk equivalent population
  - Requiring secondary prevention strategies

High Scores = High Risk
- Patients with increased plaque burdens are ~10x more likely to suffer a cardiac event over the next 3-5 years.
- For women with a CAC score ≥400, the 15-year mortality was 23.5%.

What about Very High scores?
- Asymptomatic individuals with a very high CAC score (≥ 1000) followed for 17 ± 11 months.
  - Patients with scores ≥ 1000 experienced an annual event rate of 25% for hard cardiac events (!!!)
  - MI and death

Calcium Scoring for Diagnosis/Identification
Population vs. Personalization

- Calculators work for Populations, but do they work for all individuals?
- And do our calculators even work for populations?

The Ideal Risk Assessment Tool

- Identify patients supposedly at risk, but really at low risk
  - To save them from unnecessary medications and procedures
- Identify patients thought to be low risk, but whom are really high risk
  - To institute appropriate preventive therapy

Is CAC better at identifying risk?

“Low Risk”

- “Low Risk” Women (by ACC/AHA PCE)
  - <7.5% risk by Pooled Cohort equation
- 36% had positive CAC scores.
  - ~3-fold higher risk of cardiac event
- Scores >100 found in 10% of patients
- Very high CAC scores (≥400) found in 3-5%

Is CAC better at identifying risk?

“Intermediate Risk”

- ~40% of “Intermediate Risk” patients (5-7.5% risk) by ACC/AHA Pooled Cohorts had CAC = 0
- 18% of patients >75yo had scores = 0

Is CAC better at identifying risk?

“High Risk”

- Only 22% of patients deemed “High Risk” by ACC/AHA Pooled Cohorts had CAC>300.
  - Only 42% had CAC>100
Is CAC better at identifying risk? “High Risk”

- Approximately 1 out of 5 patients with a PCE prediction of >15% ten year risk actually had CAC = 0
- 20% of patients thought to be high risk were really extremely low risk

Mortensen et al. JACC 2016;68(9):881-7

The Number Needed to Screen (NNS) in the “High Risk” (>15% PCE) group to find 1 patient with a CAC = 0
- 4.5
- In the “Intermediate Risk” group (7.5%-15% PCE)
  - NNS = 2.6

Re-Classified Patients

- 1 out of 7 patients had significant disagreement/discrepancy between risk predicted by CAC and by Pooled Cohorts.

Isma'eel et al. Am J Cardiol 2016;118:1480-5

Re-Classified Patients

- In the patients who could be re-allocated to a low-risk group because of a score of 0:
  - The event rate was just 1% over five years
  - Truly low risk
- In the group reclassified as high risk:
  - There was an event rate of >8% over five years
  - Truly high risk

Erbel RA et al. ACC Scientific Sessions 2009

Is CAC better at identifying risk in patients with DM?

- Diabetes
  - Is DM truly an anginal equivalent?
    - 25-30% of diabetics have no evidence of CAD
  - Patients with DM and no evidence of CAD by coronary CTA did not exhibit an increased risk of death
    - compared with the propensity-matched nondiabetic subjects

Rana et al. Diabetes Care 2012;35:1787-94

Risk Stratification

Calcium Scoring vs. Risk Calculators
Why? Because Risk Factors Stink

- The poor discriminatory power of risk factors was demonstrated in 542,008 patients presenting with a first myocardial infarction:
  - 14.4% had 0 RFs
  - 34.1% had 1 RF
  - 31.6% had 2 RFs
  - 15.4% had 3 RFs
  - 4.1% had 4 RFs

Canto JG et al. JAMA 306:2120–7

Will a Calcium Score Change Management?

Change in Management Strategy

- For patients previously considered high risk with negative scores
  - Can downgrade therapy through Shared Decision-Making process

- For patients previously considered low risk that have positive scores
  - Counsel accordingly and start therapy

CAC = 0

- Data suggest that aggressive management in this cohort is not warranted
  - "downgrade therapy"

- What does that mean?
  - Up to one-third of the statin-eligible population would do well without chronic medical therapy and would be effectively treated with lifestyle changes alone

High Score

- A score of >100 (or >75th percentile) would yield a post-test probability in the majority of patients >2%/yr
  - Event rate ≥ 20% over 10 years
- Re-classifies the patient within the range of a CHD risk equivalent population
- Requires secondary prevention strategies

Patients care about their score

- CAC has been shown to positively affect initiation of and adherence to medication and lifestyle changes
  - In 505 asymptomatic patients, statin adherence >3yrs after visualizing their CAC scan:
    - 90% in those with a CAC score >400
    - 44% in those with a CAC score of 0

EISNER Trial

- CAC-directed care produced significant improvement in systolic blood pressure, low-density lipoprotein cholesterol, weight, waist size, and FRS compared with usual care, without an increase in downstream testing.

Patients care about their score

- 980 asymptomatic subjects followed for 3 years
- Significant increases seen in:
  - Exercise
  - Aspirin therapy initiation
  - Dietary changes
- Highest in patients with CAC scores >400

Calcium Scoring is Cost-Effective

- Primary Prevention Setting:
  - Calcium scoring in at-risk men (age 40-50yo), was modeled to cost $37,633 per quality-adjusted life year saved.
    - Assuming a 30% improvement in survival
      - Usual benefit of a statin
  - Most patients would prefer to pay for an imaging test than take a pill every day for life

- Among those with 10-year estimated risk of 6% to 20%, decision to avoid treatment among those with CAC=0 versus treat-all approach with generic statins is cost-effective, as long as CAC testing is priced < $235.
**Calcium Scores and Stress Testing**

- ACC/ASNC appropriateness criteria state that a zero calcium score precludes the need for nuclear stress testing.
- Represents a potential huge cost savings for the US health care system.

**Calcium Scoring: Pros**

- Fast
- No contrast
- Low radiation dose
- Cheap
  - $150
  - Cheaper than NMR, Stress Tests, etc.
  - Just not covered by insurance

**Calcium Scoring: Cons**

- Costs of Potential Downstream Testing
- Radiation Exposure

**A Word About Radiation**

**Average Radiation Doses**

- Avg Background radiation in US: 3.0 mSv/yr
- Chest x-ray: 0.05 mSv
- Mammogram: 0.8 mSv
- Chest CT: 7 mSv
- Nuclear Stress Test: 15 mSv
- “Low Dose” Lung CA screen CT: 1.5 mSv
- 64-slice Calcium Score: ~1 mSv

If we REALLY care about radiation exposure…
Does the patient even need another test?

- We can prevent unnecessary radiation exposure by using info from available studies before ordering new ones
  - ~ 600,000 3 mm ECG-gated CT scans done in the United States annually
  - >7.1 million 6 mm lung CT scans are done annually for other clinical indications

- 40-45% of patients undergoing CT Chests had potentially clinically significant cardiovascular findings and coronary calcifications that went unreported.

- CAC >0 was present by expert reader interpretation in 108 of 201 (53%) nongated noncontrast CT scans in patients without suspected CAD
  - But was reported by the radiologist in only 69% of the 108 positive scans

- CAC scores on standard 6 mm chest CTs are strongly correlated with 3 mm ECG-gated CTs
  - Similarly predict mortality in community-living individuals.

Chest CTs performed for other clinical indications may provide an untapped resource to garner CVD risk information without additional radiation exposure or expense.

A Question:

- Is there another test that almost half the population gets on a yearly basis that can help us risk stratify our patients?
Mammography to Screen for CAD?
- There is a strong quantitative association of Breast Arterial Calcification seen on Digital Mammography with CAC.
- Positive predictive value of nearly 70%-80% for identifying women with presence of CAC.
- BAC is superior to standard cardiovascular risk factors.
- BAC is equivalent to both the FRS and PCE for the identification of high-risk women.

A Thought Experiment
- Assume a conservative estimate of 10% of mammograms with Breast Arterial Ca²⁺
- Approximately 4 million women nationwide undergoing screening mammography will exhibit Breast Arterial Ca²⁺
- 2 to 3 million of them will likely have signs of premature CAD.

Conclusion
- Risk Calculators are useful for populations
- Individualized tests like Calcium Scoring tell you accurate, prognostic information about the patient in front of you
- They are cost effective
- Minimal radiation
- Motivating

Final Thoughts

Editorial Comment #1
Population vs. Personalization

Population Medicine
Do we even need risk assessment at all?
Population Medicine:
Empiric Treatment of all patients?

- According to the 2013 ACC/AHA guidelines, everyone with optimal levels of risk factors will qualify for statin therapy if they live long enough (using 7.5% threshold).
  - AA men at age 66
  - AA women at age 70
  - Non-AA men at 63
  - Non-AA women at 71

- Some have suggested universal therapy with statins starting at age 55yo

Population Medicine

- “In the setting of low cost/well tolerated statins, there is little role for Calcium Scoring”
  - Currently Calcium Scoring has a Class IIb recommendation as a result

Editorial Comment #2:
A Curiosity of our Culture

- Atherosclerotic vascular disease accounts for more death and disability than all types of cancer combined
- Cancer screening is recommended, calcium scans are not
  - Colonoscopy: 0.1-0.3% serious adverse event rate
- $4.9 Billion on Cancer Research by NCI annually
- $2 Billion spent on CV research by NIH annually

The End

- “The greatest danger to any society is a failure to embrace new ideas”
  - Franklin Delano Roosevelt