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Will The Coronary Calcium Score Affect the Decision To Treat With Statins?

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Disclosures

- No financial relationships relevant to this presentation

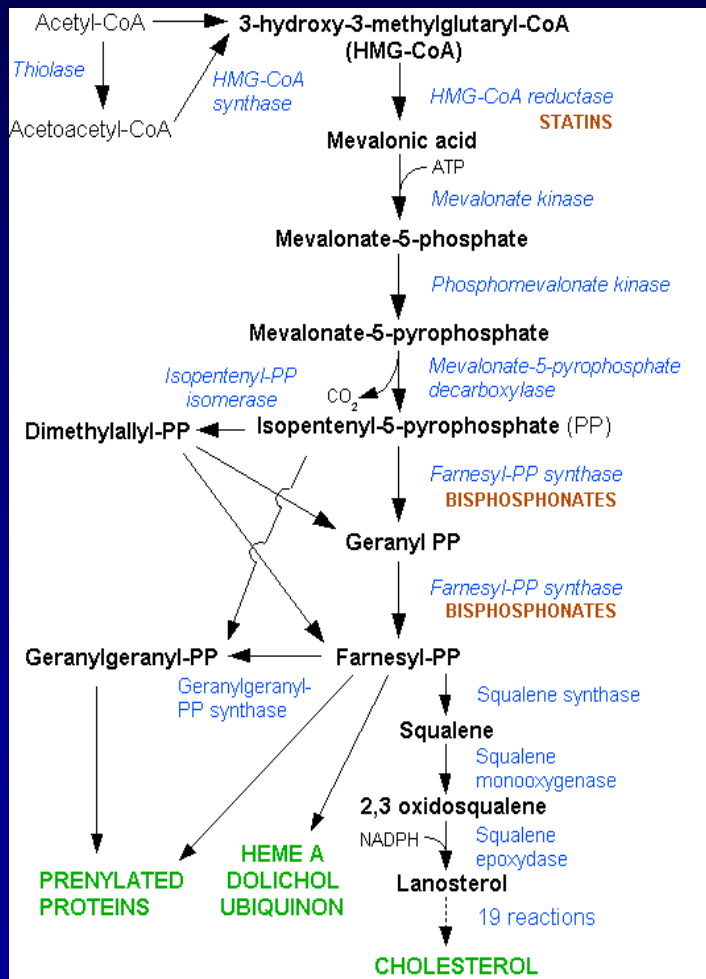


Objectives

- Identify which patient populations are currently eligible for treatment with statins
- Discuss evidence behind the efficacy of statin therapy
- Outline traditional means of cardiovascular risk stratification
- Brief background on coronary calcium scoring
- *The yin* - why coronary calcium scoring will impact treatment with statins and should be employed
- *The yang* – why coronary calcium scoring will have little impact on statin therapy and cardiovascular outcomes and should not be employed



Statins – Mechanism of Action



- Statins (HMG-CoA reductase inhibitors) block conversion of HMG-CoA to Mevalonic Acid, resulting in decrease in cholesterol synthesis
- Statins can reduce LDL 10-60%
- Statins have more modest effects on HDL and triglycerides
- Statins are also postulated to have numerous additional “pleiotropic” effects independent of effects on cholesterol



What Patient Populations Are Currently Treated With Statins?

- Primary prevention
- Secondary prevention
- Acute ischemic syndromes



Primary Prevention

- Asymptomatic individuals without overt cardiovascular disease, but with hyperlipidemia or other traditional risk factors for cardiovascular events
- Multiple large randomized clinical trials have suggested a relative risk reduction in first CV event of >30% with long term statin therapy
 - WOSCOPS Study 1995
 - AFCAPS/TEXCAPS Study 1998
 - JUPITER Study 2008



Secondary Prevention

- Patients with symptomatic coronary artery disease, peripheral arterial disease or cerebrovascular disease treated for prevention of recurrent events
- A number of randomized controlled trials have shown a 13-30% relative risk reduction in all cause mortality in patients with established cardiovascular disease treated with statins
 - 4S Study 1994 -- Post CABG Trial 1997
 - Care Study 1996 -- Heart Protection Study 2002



Acute Ischemic Syndromes

- Patient with acute coronary (or cerebrovascular) events generally treated with high dose statins in the acute setting
- Randomized controlled trials suggest a decreased incidence of recurrent cardiovascular events in the short term with intensive lipid lowering therapy
 - MIRACL Study 2001
 - PROVE-IT TIMI-22 Study 2004
 - A to Z Study 2004



Statins: Costs & Side Effects

- Statins cost \$1-5 per pill. Assuming \$2 per pill, this translates to \$730 per year of treatment
- Incidence of "benign" myalgias in large clinical trials of statin therapy range from 2-11%
- Clinically significant myopathy, defined as a serum CK elevation >10 times normal in association with muscle symptoms, occur in less than 0.5% of patients in the large clinical trials
- The average incidence of hospitalization for rhabdomyolysis is 0.44/10,000 patient-years
- Reported deaths due to statin-induced rhabdomyolysis have averaged 0.15 per million prescriptions dispensed in the US
- Clinical studies of statins have demonstrated a 0.5 to 3% occurrence of persistent elevations in liver enzymes



Which of These Patient Populations Will Be Impacted By Calcium Scoring?

- The main patient population who would be affected by CAC scoring is the pool of asymptomatic patients who could be treated for primary prevention
- In addition, one could use calcium scoring in patients with established disease to assess for disease progression or response to therapy



Currently How Do We Decide Which Patients to Treat With Statins?

- Overall clinical impression in the office?
- NCEP/ATP Cholesterol Treatment Guidelines?
- Risk calculators – Framingham and others?
- Calcium scoring, Carotid IMT, biomarker tests such as CRP?



Lipid Therapy - Guidelines

- Guidelines have evolved dramatically from the 1980s when serum cholesterol of 300 mg/dl was considered acceptable
- In part this is related to awareness of relationship between cholesterol and CV risk
- Most recent update to cholesterol treatment guidelines is the NCEP ATP III update (2004)



NCEP/ATP III Update (2004)

- **Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):**
 - Clinical CHD
 - Symptomatic carotid artery disease
 - Peripheral arterial disease
 - Abdominal aortic aneurysm
 - Diabetes
- **Determine presence of Major Risk Factors That Modify LDL Goals:**
 - Cigarette smoking
 - Hypertension (BP >140/90 mmHg or on antihypertensive medication)
 - Low HDL cholesterol (<40 mg/dL)
 - Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
 - Age (men >45 years; women >55 years)
- **If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (Framingham or other risk calculator).**



ATP III 2004 Update

Risk category	LDL goal	LDL level at which to initiate therapeutic lifestyle changes	LDL level at which to consider drug therapy*
High risk: Coronary heart disease (CHD) or CHD risk equivalent (10-year risk >20 percent)*	<100 mg/dL (2.58 mmol/L); optional goal <70 mg/dL (1.82 mmol/L) in very high risk Δ	≥ 100 mg/dL (2.58 mmol/L) $\diamond \geq$	100 mg/dL (2.58 mmol/L) \S ; <100 mg/dL (2.58 mmol/L) consider drug options
Moderately high risk: 2 or more risk factors (10-year risk 10 to 20 percent) \yen	<130 mg/dL (3.36 mmol/L) \ddagger	≥ 130 mg/dL (3.36 mmol/L) $\diamond \geq$	≥ 130 mg/dL (3.36 mmol/L); 100 to 129 mg/dL consider drug options $\ $
Moderate risk: 2 or more risk factors (10-year risk <10 percent) \yen	<130 mg/dL (3.36 mmol/L)	≥ 130 mg/dL (3.36 mmol/L)	≥ 160 mg/dL (4.13 mmol/L)
Lower risk: 0 to 1 risk factor**	<160 mg/dL (4.13 mmol/L)	≥ 160 mg/dL (4.13 mmol/L)	≥ 190 mg/dL (4.91 mmol/L); 160 to 189 mg/dL consider drug options



Framingham Risk Score

- Original Framingham Risk Score published 1998
- Used a derivation and validation cohort from the Framingham Heart Study
- Incorporates age, gender, Total Cholesterol, HDL-cholesterol, systolic blood pressure (whether the patient is treated or not), diabetes, and smoking to derive an estimated 10 year risk of having a cardiac event
- The original FRS was modified in 2002 by ATP III for use in their recommendations for treatment of dyslipidemia
- The modifications include elimination of diabetes, broadening of the age range, and inclusion of hypertension treatment



Framingham Risk Calculator

- Age: (Years)
- Gender: (Female/Male)
- Total Cholesterol: (mg/dL)
- HDL Cholesterol: (mg/dL)
- Smoker: Yes/No
- Systolic blood pressure: (mm Hg)
- Currently on any medication to treat high blood pressure: Yes/No



Framingham Risk Stratification

- Low risk (<10 percent CHD risk at 10 years)
(82 percent of patients)
- Intermediate risk (10 to 20 percent CHD risk at 10 years)
(16 percent of patients)
- High risk (>20 percent CHD risk at 10 years)
(3 percent of patients)



Other Risk Scoring Systems

- **Euroscore (SCORE):**

- Derived by pooling 200,000 patients from cohort studies in 12 European countries.
- Variables incorporated into the model included age, gender, systolic blood pressure, total cholesterol, HDL cholesterol, and cigarette smoking. The mean follow-up was 13 years, with the end point being cardiovascular death.
- Advantage over FRS is it estimates the ten year risk of any first fatal atherosclerotic event (e.g. stroke or ruptured abdominal aneurysm), not just coronary heart disease-related deaths

- **Reynolds Risk Score:**

- The Reynolds risk score for men was developed from a prospective cohort of over 10,000 American men without diabetes and a similar model was ultimately developed for women.
- Like the Euroscore, it also includes stroke as a CV outcome
- Advantage over FRS: RR score includes all the variables in the Framingham risk scores as well as the level of high sensitivity C-reactive protein (CRP) and parental history of MI before age 60, and includes stroke as a cardiovascular outcomes



The Problem With Current Models Of Cardiovascular Risk

- The Framingham Risk Score and other risk calculators remain imperfect in prediction of CV risk
- The stakes are high - cardiovascular disease is the leading cause of death in industrialized nations
- With the current epidemic of obesity, diabetes and dyslipidemia, we need to improve models of risk prediction



Scope of the Problem

- For 150,000 patients/year in the USA, a fatal heart attack is the first sign of CV disease
- 50% of MIs occur in patients with no prior history of CV disease
- A large proportion of patients presenting with a first MI would not qualify for lipid lowering therapy under current guidelines
- This has led to a search for additional screening modalities which might improve on current risk stratification



Properties of a Screening Test

- Excellent sensitivity and NPV
- There should be available therapy that modifies the disease once disease is detected earlier with a screening test
- A high level of evidence that screening affects clinical outcomes
- Screening tests should be cost effective
- Does coronary calcium scoring fulfill these criteria?



Coronary Calcium - Historical Background

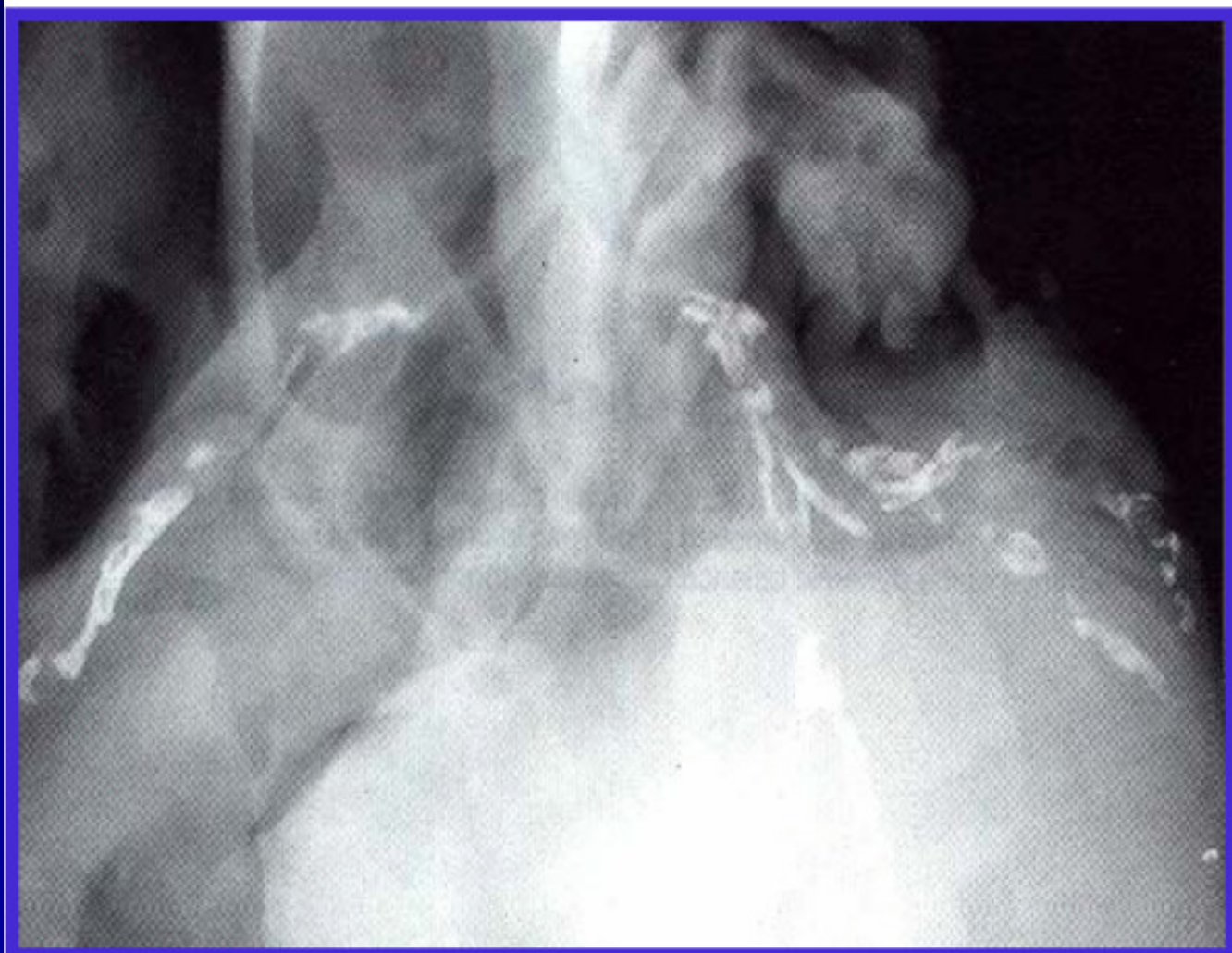
- **1700:** First pathologic reports of coronary sclerosis and calcification by Bellini in Italy and Thebesius in Germany
- **1850:** Cruveilheir described “gangrene” of the myocardium following “calcareous infiltration” of the mouth of the coronary artery
- **1903:** First plain radiographs of calcified coronary arteries published by Simmonds in London
- **1959:** Blankenhorn and Stern first described detection of coronary artery calcification with fluoroscopy
- **1970s:** CT technology introduced. CT better suited than fluoroscopy or plain radiographs for detecting and quantifying coronary artery calcium (CAC)

Blankenhorn, DH, Stern, D. Am J Roentgenol Radium Ther Nuc Med 1959. 81: 772



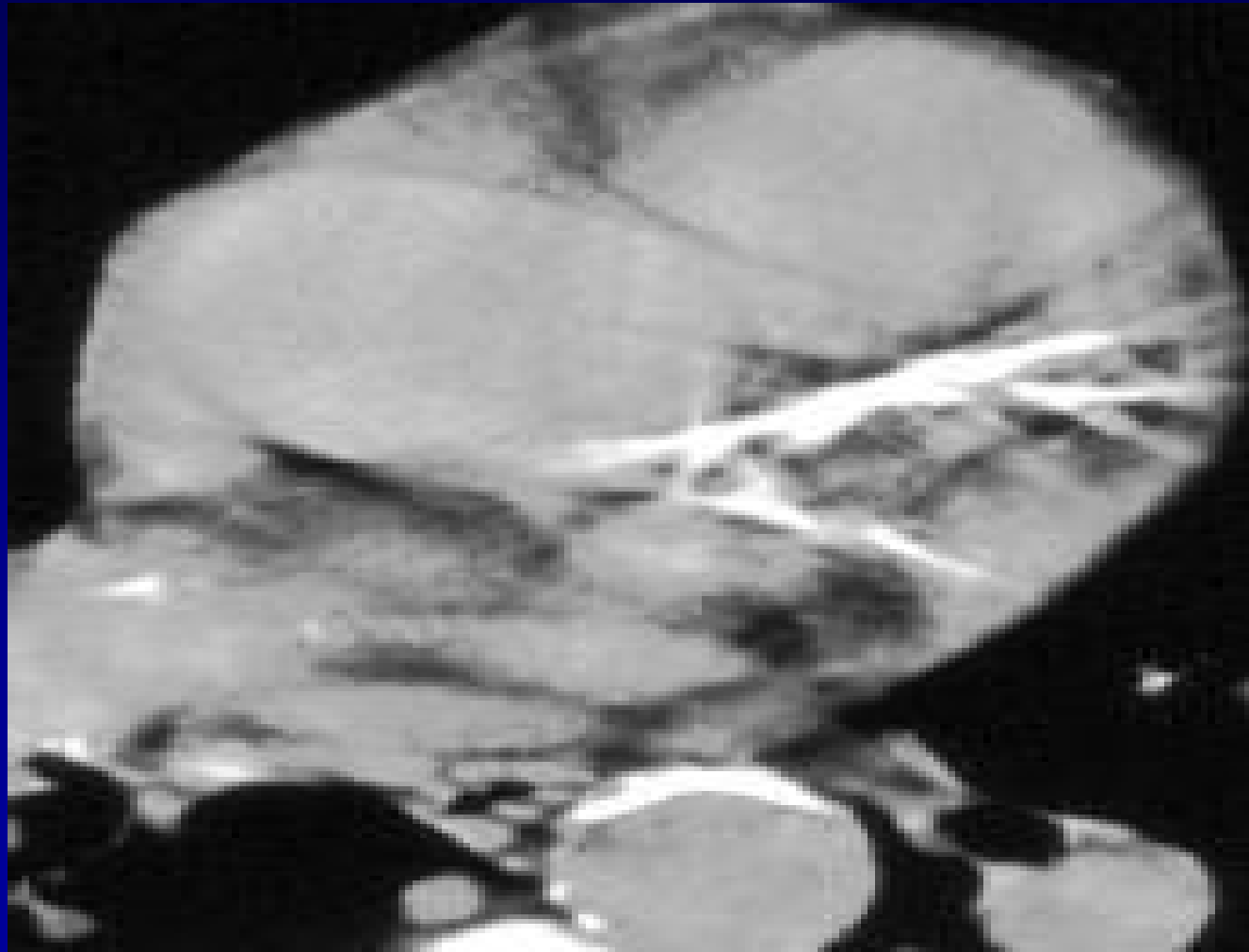
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Coronary Calcium on Plain Film



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Coronary Calcium on CT



Coronary Calcium - Historical Background

- **1980:** Margolis et al. first reported an association between coronary calcification on fluoroscopy and future coronary events
- **1980s:** Development of electron beam CT (EBCT) permitted the more rapid acquisition of images with increased temporal resolution resulting in decreased artifacts from cardiac and patient motion
- **1990:** Agatston published standardized protocol for quantification of coronary artery calcium
- **Late 1990s-today:** Newer multi-detector CT (MDCT) units available and in widespread use allowing rapid acquisition times, similar to EBCT
- **Today:** CAC scoring frequently done (but not reimbursed) using both MDCT and EBCT. It should be noted the vast majority of clinical studies of CAC used EBCT, but newer studies have demonstrated that CAC scores derived using MDCT and EBCT are generally equivalent

Margolis, JR et al. Radiology. 1980; 137: 609

Agatston, AS et al. J Am Coll Cardiol. 1990; 15: 827-32



Pathophysiology

- Calcification of the coronary arteries is an active process and occurs almost exclusively as part of the development of atherosclerosis
- CAC is almost universally absent in the normal vessel wall
- Although calcification is sometimes seen in early atherosclerotic lesions, it is most commonly seen in complex lesions and in older age
- Calcification is seen very frequently in plaques that have evidence of healed plaque rupture by histology



The Yin – Why CAC Scoring Will Impact The Decision To Treat

- CAC scores are independently associated with future cardiovascular events
- A negative CAC score has a very high sensitivity and NPV for excluding coronary atherosclerosis
- CAC scoring has been shown to improve on traditional risk stratification in several patient cohorts
- CAC scoring allows assessment of the presence of atherosclerosis rather than risk factors in any individual patient
- Serial measurement of CAC scores may be used as a better measure of efficacy statin of therapy in patients with established disease



CAC Score Is An Independent Predictor of Future CV Events

- **Arad et al.** studied 1173 asymptomatic patients self/physician referred for CAC scoring with 19 month and 3.6 year follow up. Baseline CAC score was highly predictive of cardiovascular events after adjustment for self-reported risk factors
- **Kondos et al.** demonstrated the predictive value of CAC scoring in 8855 self referred asymptomatic men and women. Follow up at 37 months was available in 64% of patients and suggested CAC was independently predictive of CV events beyond conventional risk factors
- **Prospective Army Coronary Calcium Project** enrolled young, asymptomatic men and women with mean age 43 years. The presence of CAC was associated with 12 fold increase in 3 year risk of CV events
- **Rotterdam Coronary Calcification Study** prospectively enrolled 1795 elderly patients. CAC was independently associated with event rate and total mortality



CAC Score Improves On Traditional Risk Stratification In Multiple Populations

- **Greenland et al.** prospectively studied 1461 asymptomatic patients from the South Bay Heart Watch Study, with follow up to 8.5 years
 - A CAC score of 0 vs. a score of 300 was predictive of CV events (HR 3.9).
 - CAC score modified the risk assessment for all FRS categories other than low risk (<10% risk)
- **Polonsky et al.** evaluated the extent to which CAC scoring added to traditional risk score in the MESA cohort
 - In a model using CAC in addition to risk factors, there was a significant improvement in 5 year risk prediction
 - An additional 23% of patients who experienced events were correctly classified as high risk and an additional 17% of patients who did not experience events were classified as low risk



CAC Score Improves On Traditional Risk Stratification

- CAC scoring is therefore complimentary to traditional risk stratification, allowing us to more accurately classify patients in the intermediate risk category
- This can be done based on the combination of the CAC and FRS or by substituting a “vascular age” for chronologic age in the Framingham risk calculator, as suggested by Nasir et al.



CAC Scoring Individualizes The Decision To Treat

- Though Framingham and other risk scores are useful on a population level for predicting who will develop CHD, they evaluate risk factors and cannot determine whether an individual patient already has CHD
- Knowledge of the presence or absence of calcified plaque often changes a patient's threshold or willingness to accept statin therapy
- Similarly, studies have demonstrated higher rates of compliance with statin therapy in patients with high calcium scores versus those with low or no calcium



CAC Scoring Could Reduce The Need For Statins in Some Patients

- Identifying intermediate risk patients by FRS who are in fact lower risk (negative CAC score) would cut costs and the burden of medications for this patient sub-group
- In high risk patients by FRS who have negative CAC and are intolerant of statins, could we not counsel them that they might come off therapy?



Adjusting Statin Therapy Based on Treatment Response

- In the current era, CAC scores are very reproducible with generally <15-20% inter-scan variability
- Observational studies have suggested that CAC scores progress in untreated patients whereas in those aggressively treated with statins, they remain stable or in fact regress
- Thus, serial CAC scoring may provide a means of evaluating true treatment response at the end-organ level and may be a more appropriate endpoint for titrating statin dose than LDL



Costs and Radiation Exposure of CAC Scoring Are Not Prohibitive

- Current charges for CAC scoring are ~\$400
- However, if widely employed, costs would undoubtedly fall
- With current technology, and prospective acquisition, CAC scoring can be done with minimal radiation exposure (1-2 MsV)



The Yang – Why CAC Scoring Should Not Impact The Decision to Treat

- CAC scoring actually has a relatively low sensitivity for detecting atherosclerosis seen at autopsy
- Doubts remain over reproducibility of calcium scoring
- Methodological issues surrounding studies evaluating CAC scoring and CV outcomes
- A relatively small segment of the population (intermediate risk) will be impacted by CAC scoring
- Questions exist over cost effectiveness – would it be cheaper just to treat intermediate risk patients?
- Doubts over predictive value of CAC in non-Caucasian populations
- CAC scores have been shown to progress even on statin therapy
- CAC scoring carries a real radiation exposure making it a suboptimal screening modality, particularly for young women



Lower True Sensitivity of CAC Scoring?

- Though we imagine that a lack of CAC largely excludes atherosclerosis, autopsy studies have suggested that CAC has a much lower sensitivity for detecting atherosclerosis on histology
- The calcified plaque burden by CT represents as little as one fifth of the total plaque area seen on histology
- Therefore, are we truly being consistent in stating that patients without CAC are free of atherosclerosis and thus should not be treated?



Are CAC Scores Reproducible?

- Most of the evidence supporting use of CAC comes from EBCT studies whereas MDCT is now widely employed – though scores on each system are felt to be similar in terms of prognosis, there are nonetheless differences between EBCT and MDCT-derived scores
- Variability in CAC scores obtained at the same visit may be >20% and as high as 43% with the largest variability coming at higher scores, which is the group at highest risk



Methodological Issues Exist With Many of the Studies Suggesting the Value of CAC

- Many studies have used self-referred or convenience samples, rather than prospective cohort studies like Framingham
- Most studies correlating CAC with stenosis at catheterization are impacted by fact that the scanned patients were high enough risk to justify angiography
- Many other studies using revascularization as an outcome suffer from workup bias



CAC Scoring Does Not Improve Significantly on Traditional Risk Stratification

- By Bayesian theory, low risk patients will almost certainly remain low risk regardless of CAC scoring, and the same holds true for high risk patients
- In the latter group, it is unlikely that a negative CAC score will or should prevent aggressive medical therapy with statins
- Therefore, the intermediate risk category (a relatively small group) is the only one which is meaningfully impacted by CAC
- In one study of intermediate risk patients, >60% were already on statin/ASA per the original ATP III guidelines



CAC Has Not Been Well Studied in Non-Caucasian Populations

- Most studies of coronary calcium have enrolled predominantly white men
- Although MESA provides some information with regard to CAC in other ethnicities, does sufficient data exist to validate basing treatment decisions on CAC in these populations?
- For example, African Americans in general have lower CAC relative to Caucasians despite significantly higher relative burden of atherosclerosis



CAC Scoring and Treatment Response

- Little data exists on modifying treatment intensity with statins based on regression of CAC at serial measurement
- Indeed, several recent randomized controlled trials have shown that statins do NOT regress coronary calcium scores
- These patients should already be targeted for maximal medical therapy and the lowest LDL target achievable



CAC Is Not Cost Effective

- Rather than performing coronary calcium scoring on the entire intermediate risk cohort, should we simply treat the intermediate risk patients with statins
- A cost-benefit analysis by Diamond & Kaul suggested that using CAC scoring in addition to FRS would be less cost-effective than simply treating all patients at intermediate risk in terms of cost per life/year saved



CAC Does Not Fulfill Remaining Criteria of A Screening Test

- CAC scoring carries with it a radiation risk of at least 1-2 mSv and possibly several fold higher depending on equipment/protocol
- With repeated examinations, this exposure could be significant, particularly for younger patients and women
- No prospective randomized trials have shown that instituting CAC scoring changes clinical outcomes



Where Does The Truth Lie?

- As usual, somewhere in-between the 2 sides of this presentation!
- A growing weight of evidence exists to support the use of CAC scoring in intermediate-risk patients
- Use of CAC scoring can help to individualize treatment decisions with statins based the presence or absence of atherosclerosis rather than risk factors
- Little prospective randomized data exists to suggest CAC scoring impacts CV outcomes and the weight of evidence probably does not support its use in the broader population

