How can we Intelligently Diagnose Coronary Artery Disease with so many Investigations Available Nowadays

Hong Kong Core Cardiology Certificate Course (Module 1)
July 8, 2018

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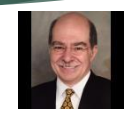
Without making an appropriate & accurate diagnosis, management will be unsound & inappropriate.

Applicable not only to CAD,

but also other disease diagnoses in day-to-day clinical practice.

George Diamond (1941-2015) was a central member of the great all-star Cedars-Sinai team of the 1970s & 1980s that included Jeremy Swan, William Ganz, and PK Shah. Diamond pioneered the use of Bayesian theorem in CV medicine, first to think about the inevitable limitations of diagnostic tests, and how they should be used in clinical practices.



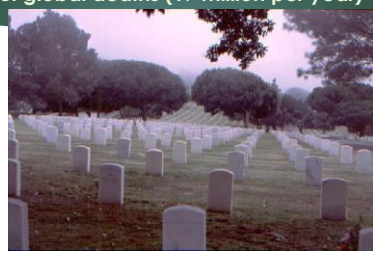
Dr Diamond's seminal work in the clinical diagnosis of CAD advanced the concept that a test's diagnostic accuracy depends on its prevalence.

- ACC Distinguished Service Award 2004

He was one of the smartest minds in cardiology who had a profound influence on the lives of virtually all who had the privilege of working with him. He was one of the brightest shining stars in our galaxy much admired for his intellect, unique insights and uncompromising stance. He was often described as the 'conscience of cardiology'. His passing will be mourned across the globe. We have lost a giant in the field of cardiology. Truly an end of an era!

- Sanjay Kaul

CV disease accounts for 30 % of global deaths (17 million per year)



By 2020, the leading cause of mortality & morbidity worldwide, accounting for 25 million deaths per year

CAD- A major public health concern worldwide

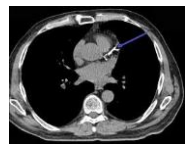
- In USA, over 17 million CAD,
  ~ 10 million has angina
- In Hong Kong, top killer as single disease entity

Common Investigations

- Blood tests, CXR
- ECG
- Exercise Stress ECG Test: Treadmill or Bicycle
- Echocardiography: Rest or Stress
- Radionuclide Imaging: Exercise or Pharmacological
- Cardiac MRI & PET
- CT Coronary Angiogram, Perfusion & Calcium Score
- Coronary Angiogram, IVUS, FFR, OCT

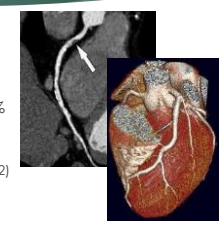
CT Coronary Calcium Score

- Correlates with coronary atherosclerosis but weakly with angiographic severity
- No correlation with plaque stability
- Age dependent for sensitivity & specificity
- **Limited incremental diagnostic value**
- **Added radiation exposure**
- **Role is inappropriate or uncertain for most situations**



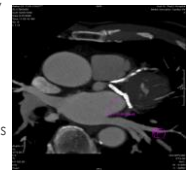
CT Coronary Angiogram

- Rapid proliferation with 64-320 slices
- **Appropriate for chest pain with intermediate pre-test likelihood**
  (Promise 2015 and 2013 ACC AUC)
- Sensitivity, specificity & accuracy ~ 90%
- **NPV in intermediate pretest probability drops with increase calcium score**
  (90% in <100, 70% in ≥400) (Core-64, 2012)
- NPV ~ 50% in high pretest probability



Limitations of CT Coronary Angiogram

- Tachyarrhythmia, motion artifacts, heavily calcified segment (10%), metallic interference (stents, pacemaker, ICD)
- Contrast: 85-100 ml
- **Radiation risk**: **average > 1/2000 cancer per study**, more with irregular rhythm, obesity, bypass graft, serial study



Radiation Risk of CT Coronary Angiogram

- **Estimated cancer risk: woman (usu. breast)**

Age 20	**1/143**
Age 40	**1/284**
Age 80	1/3261
Man Age 40	**1/1241**

(64 slices, JAMA,2007)

- Median exposure 12 mSv of radiation = 600 CXR or 2 x coronary angiogram

(64 slices, 70% with dose saving, JAMA 2009)

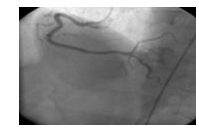
- Radiation exposure significantly decreased recent years (3-5 mSv)

For CAD Diagnosis

	Sensitivity	Specificity
Treadmill ECG	45%(68%)	85%(77%)
Radionuclide Stress Perfusion	87%	73%
Stress Echo (Exercise/Dobutamine)	86%/82%	81%/84%
CMR (Vasodilator/Dobutamine)	87%/88%	85%/90%
CT Coronary Angiogram	85%	90%

Coronary Angiogram

- **Reference standard: highest resolution of 0.1mm**
- Limitations:
  - Assess lumen only
  - Lack functional assessment e.g. ischemia, scar or viability
  - Unable to predict disease progression or plaque stability



Intelligent use of Investigations

comes from

Wisdom

comes from

Knowledge, Experience & Mistakes

Medicine is a science of uncertainty and an art of probability

William Osler

Tips 1

- **Diagnosis is only a probability**
- Nothing is absolute or 100% correct
  except GOD

Diamond & Forrester Pre-Test Probability of CAD (%) by age, sex & symptom

	Typical		Atypical		Non-anginal	
Age	M	F	M	F	M	F
30-39	76	26	34	12	4	2
40-49	87	55	51	22	13	3
50-59	93	73	65	31	20	7
60-69	94	86	72	51	27	14

ACC/AHA 2002

Tips 2

Good clinical history is critical
for an accurate pretest diagnosis

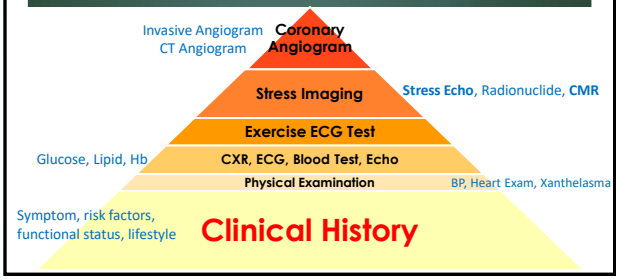
Chest Pain

- Nature: **usually dull or pressure, never sharp**
- Location: **retrosternal, precordium, epigastrium, +/- radiation; rarely R or fleeting**
- Localization: **vague, never be well localized with 1-2 fingers, size > fist or palm size**
- Duration: **30 sec-30 min, never < 30 sec (persistent pain suggests MI or non ischemic)**
- Aggravating or relieving factors: **(rest pain may be unstable)**
- **Severity, stability & associate symptoms (sweating)**

Clinical History

- **Cannot be delegated**
- **Time for history taking is the most well spent**

Diagnosis & Evaluation of CAD



Tips 3

1. **Choice of Investigation should be based on pre-test probability of disease**
2. **Pre-test diagnosis and its accuracy will significantly affect the post-test diagnosis and its accuracy**

Back to the Basics

Test Results

True Positive (TP)
- individuals with disease and a (+) test

True Negative (TN)
- individuals with no disease and a (-) test

False Negative (FN)
- individuals with disease and a (-) test

False Positive (FP)
- individuals with no disease and a (+) test

Sensitivity of a test
- % of those individuals with disease that has a (+) test
- TP/(TP + FN)

Specificity of a test
- % of those without disease that has a (-) test
- TN/(TN + FP)

Positive predictive value (PPV)
- Probability of disease after a (+) test
- TP/(TP + FP)

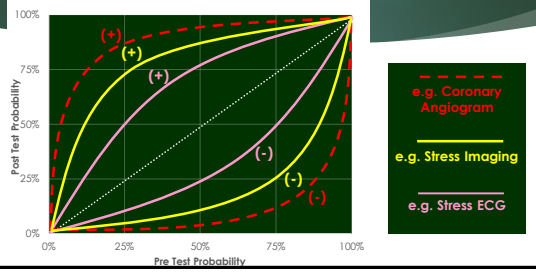
Negative predictive value (NPV)
- Probability of no disease after a (-) test
- TN/(TN + FN)

Fact

All investigations have false positive & false negative findings

No test 100% sensitive or specific

Pre test & Post test Probability of Disease



To recap

1. **For any given Ix, the post test likelihood or probability (diagnosis) is determined by the pretest likelihood (Bayesian Principle)**
2. Inaccurate pretest Dx results in inaccurate post test final Dx, no matter what & how powerful the test or Ix is
3. **Good clinical history & baseline assessment is critical for an accurate pretest diagnosis, and hence an accurate final diagnosis**

Tips 4

1. **Value of a test is greatest when pretest likelihood is intermediate**
2. **Select additional investigation that could provide significant incremental information** of value in diagnostic accuracy

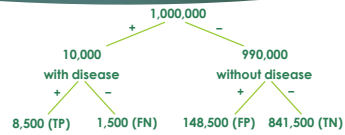
Case 1

- 35 yo healthy premenopausal woman with non-anginal chest pain
- Probability of CAD is 1% (-2%)

When 1% of population being tested have the disease

Pop tested (1m)
Pretest Prob (1%)

Stress Test
with sen 85%
sp 85%



$$PPV = \frac{TP}{TP+FP} = \frac{8,500}{8,500+148,500} = 5.41\%$$

$$NPV = \frac{TN}{TN+FN} = \frac{841,500}{841,500+1,500} = 99.8\%$$

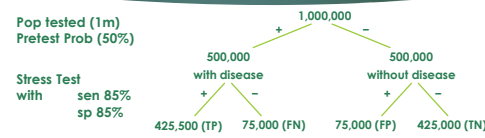
Case 1

- 35 yo healthy premenopausal woman with non-anginal chest pain. Diagnosis of CAD is 1% probability (99% non CAD).
- **No further (non-invasive) test is required or helpful. Actually it costs more harm than good.**

Case 2

- 45 yo man with atypical chest pain or
  45 yo woman with typical angina or
  65 yo woman with atypical chest pain
- Have intermediate probability/likelihood (around 50%)

When 50% of population being tested have the disease



$$PPV = \frac{TP}{TP+FP} = \frac{425,000}{425,000+75,000} = 85\%$$

$$NPV = \frac{TN}{TN+FN} = \frac{425,000}{425,000+75,000} = 85\%$$

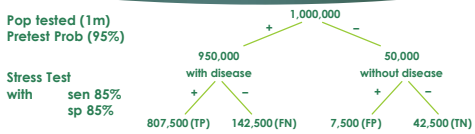
Case 2

- 45 yo man with atypical chest pain or
  45 yo woman with typical angina or
  65 yo woman with atypical chest pain
  have intermediate probability/likelihood (around 50%)
- **The test is useful to differentiate if patient has CAD, to guide treatment or if further investigations needed for definitive diagnosis**

Case 3

- 65 yo male smoker with diabetes & high cholesterol & typical exertional angina
- Pre test probability of diagnosis of CAD is >95%

When 95% of population being tested have the disease



$$PPV = \frac{TP}{TP+FP} = \frac{807,500}{807,500+7,500} = 99.1\%$$

$$NPV = \frac{TN}{TN+FN} = \frac{42,500}{42,500+142,500} = 23.0\%$$

Case 3

- 65 yo male smoker with diabetes & high cholesterol & typical exertional angina. Pre test diagnosis is >95% probability
- **No further non-invasive test!**
  Even the test is 'normal or – ', it is most likely FN.
  Invasive angiogram if revascularization is warranted or to firmly R/O CAD.

Tips 5

How to select an investigation depend on, besides pre test likelihood and incremental value of the test, **the availability, expertise, QC, cost, risks, patient condition & choice**

Conclusions I

1. **Diagnosis is only a probability**
2. **Good doctor makes accurate diagnosis**
3. **Accurate clinical history & baseline assessment is critical for an accurate pretest diagnosis**
4. **Intelligent selection of investigation requires consideration of Bayesian principle**

Conclusions II

5. **Accurate post test diagnosis is determined by accurate pretest diagnosis, no matter what test one selects**
6. **Additional test should have significant incremental diagnostic value**
7. **Also consider expertise, availability, quality control, cost, risks, patient condition & choice**